Revista Prevenção de Infecção e Saúde

The Official Journal of the Human Exposome
and Infectious Diseases Network

Agreement between qSOFA and NEWS scores in the screening of sepsis through Monte Carlo simulation

Concordância entre os escores qSOFA e NEWS no rastreamento de sepse por meio da simulação de Monte Carlo

Concordancia entre las puntuaciones de qSOFA y NEWS en el cribado de sepsis mediante simulación Monte Carlo

Miguel Damásio Cardoso Mendes[1] , Kelser de Souza Kock[1]

[1] University of do South Santa Catarina (UNISUL). Department of Medicine. Tubarão, Santa Catarina, Brazil.

ABSTRACT

Introduction: The early warning scores used for sepsis have different risk stratification and accuracy metrics, which can delay diagnosis by the health team. **Aim:** The study aims to evaluate the agreement and differences between the qSOFA and NEWS criteria in the early detection of sepsis risk in a defined population through a computer simulation. **Outlining:** A computer simulation was performed using the Monte Carlo method. 10,000 cases were simulated based on the variables described by the NEWS and qSOFA scores. **Results:** After evaluating the 10,000 cases, qSOFA≥2 proved to be less sensitive (22.22% (95% CI 21.00 – 23.49)) than NEWS≥7 (93.41% (95% CI 91.72 – 94.78)). When analyzing specificity, NEWS≥7 (62.99% (CI 95% 61.98 – 63.98)) was lower than qSOFA≥2 (98.83% (CI 95% 98.52 - 99.08)). Agreement was 66.08% (95% CI 65.15 - 67.00). **Implications:** The study showed good agreement between the scores and also showed that NEWS is superior to qSOFA when analyzing sensitivity, but the result is reversed when talking about specificity.

DESCRIPTORS

Sepsis; Computer Simulation; Organ Dysfunction Scores; Diagnostic Techniques and Procedures; Sensitivity and Specificity.

Corresponding author:
Kelser de Souza Kock
Address: 787 José Acácio Moreira Avenue.
Dehon District - Tubarão/SC.
ZIP-Code: 88704-900
Telephone: +55 48 99996 9811
E-mail: kelserkock@yahoo.com.br

INTRODUCTION

The concept of sepsis and its identification have been changing over the years and, up to early 90s, was unclear and non-objective. In 1991, a consensus defining sepsis as a systemic inflammatory response (SIRS) due an infection was drawn up. It was characterized through the clinical criteria of SIRS, associated with two or more of the following 5 variables (although there may be other manifestations): temperature >38°C or <36°C; HR (heart rate) > 90 bpm; RR (respiratory rate) > 20 bpm (breaths per minute); Lymphocytes > 12000 or < 4000 or > 10% of immature forms; $PaCO_2$ (arterial carbon dioxide pressure) < 32 mmHg (millimeters of mercury).[1]

In 2001, 10 years after the first consensus, a review of the definition criteria was carried out, due the low sensibility acquired in the precocious sepsis identification. In this document, the list of criteria, amongst them, general, hemodynamic, inflammatory, organic and tissue-related ones were added to initial criteria.[2]

15 years after the last consensus, in 2016 the "Third International Consensus Definitions for Sepsis and Septic Shock – Sepsis-3" was held, which established a new definition of the term "sepsis". It has been instituted as a deregulated inflammatory response of human body, triggered by a pre-existing infection, which may lead to complications (such as septic shock) and even death.[3]

In addition to being an extremely serious syndrome, its incidence, mortality, and lethality is extremely relevant. In 2017, 48.9 million cases of sepsis were estimated worldwide. And, 11 million related deaths, representing 19.7% of all deaths.[4] Brazil displayed an average prevalence rate of 51.3 per 100,000 inhabitants in the 2010 to 2019 period, with a lethality of nearly 55%[5], and it has been following the world trend, with an increase in the hospitalizations in the Intensive Care Units (ICU) due the syndrome, jumping from 19.4% in 2010 to 25.2% in 2016.[6]

This increase of incidence may be justified by some factors, as the augment of life expectancy, which means more populations susceptible to the condition, such as the elderly, and, also, the efforts of several public health institutions to precociously detect sepsis, leading to greater reporting and diagnosis.[7]

In addition to the public health problem, there are economic ones. The costs of sepsis and its progression to severe sepsis and septic shock increase dramatically with increasing severity of the problem.[8] In a systematic review on the hospital cost of sepsis, it was shown that the ICU stay for sepsis can vary from $10,942.47 to $79,769.[9] This means that low- and middle-income countries, which invest less in health, account for 85% of all cases in the world.[4,10]

The update called "Sepsis-3" emerged as a way to identify and establish early treatment for patients in the course of infection at risk of unwanted outcomes typical of sepsis, adapting, from the existing SOFA score (Sequential [Sepsis-Related] Organ Failure Assessment Score), a new system of criteria that would be used in prehospital care, emergencies, or hospitals without ICU. This new system is called quickSOFA (qSOFA). It consists of 3 variables, 2 of which must be positive to start the measurements: RR ≥ 22 bpm; SBP ≤ 100 mmHg; Mental confusion (yes or no).[3] The qSOFA, within the situations for which it was indicated, proved to be superior to the SOFA itself.[11]

Another widely used criterion is NEWS (UK's National Early Warning Scores).[12] It was created in 2012, adapted from the existing EWS's (Early Warning Scores) score and is part of a system known as "track and trigger", which consists of assessments of the patient's physiological parameters to quickly detect changes that could indicate decompensation (track) and trigger the team for early treatment (trigger). This same criterion proved to be more effective than other EWS for detecting cardiovascular events and unexpected hospitalizations in ICUs,[13] showing that, associated with adequate clinical judgment, it is a

very reliable method for detecting early clinical deterioration.[14]

It was implemented in several health systems and also started to be used for frameworks such as the early detection of sepsis.[15] NEWS is based on 7 criteria: Temperature; HR; RR; SBP (systolic blood pressure), PsO2 (Peripheral oxygen saturation); use of Oxygen therapy; Level of Consciousness. It establishes parameters and scores them from 0 to 3, and, through the sum, it is possible to infer the level of risk of sepsis in patients with infection.

It is also important to mention that the implementation of new strategies for tracking and diagnosing sepsis are constantly being updated, such as the NEWS 2[16] score update and the use of biomarkers such as C-reactive protein, procalcitonin, lactate, among others.[17]

Computer simulations are widely used in medicine. They have the ability to create situations similar to reality, but allow the researcher to change variables so that they become close to what is seen in everyday life.[18]

One these methods is known as the "Monte Carlo Method". This method has a mathematical and statistical character and uses random numbers within a predefined range (average value and standard deviations) and distributes them within a desired situation. This means that several scenarios can be developed and changed, generating numerous hypothetical situations, opening up an almost infinite range of options.[19]

Over the years, the theme "sepsis" has become more studied since the incidence of this condition continues to grow and its impact on public health and economy is very relevant. As there still no gold standard test for its early diagnosis, several tools were and have been created for this purpose. Therefore, the present study aims to evaluate the agreement and differences between qSOFA and NEWS criteria in the early detection of sepsis risk in a population defined through computational simulation.

METHOD

A diagnostic accuracy study was carried out through a computer simulation using the Monte Carlo method. 10,000 cases were simulated based on the variables described by the NEWS and qSOFA scores. The generation of numbers was performed using Microsoft Excel software. All simulated cases were included in the study.

For the variables bellow, random numbers with normal distribution (Gaussian) were generated, using the data of mean and standard deviation:

- Respiratory Rate: 18 brpm (Standard Deviation – 4irpm)
- O2 Saturation: 94% (Standard Deviation – 2%)
- Axillary temperature: 36.5°C (Standard Deviation – 1,5°C)
- Systolic Blood Pressure: 130 mmHg (Standard Deviation – 30mmHg)
- Heart rate: 90 bpm (Standard Deviation – 30bpm)

For the variables bellow, random numbers with discrete distribution were generated:

- Use of oxygen therapy: 70% YES – 30% NO
- Conscious state: 70% Glasgow 15 (Alert) – 30% Glasgow <15 (being related to V: responds to verbal command; P: responds to painful stimulus or U: unresponsive).
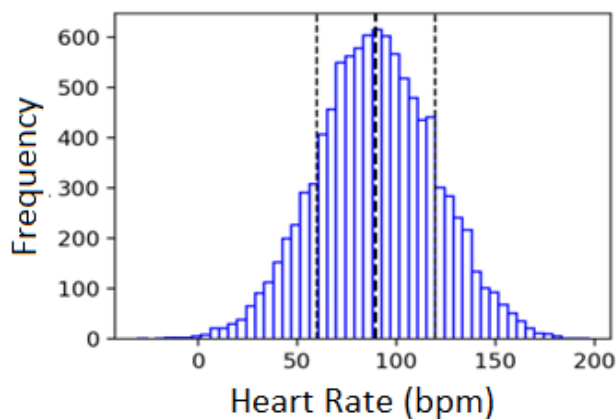
Figures 1 through 7 represent the distribution of these variables:

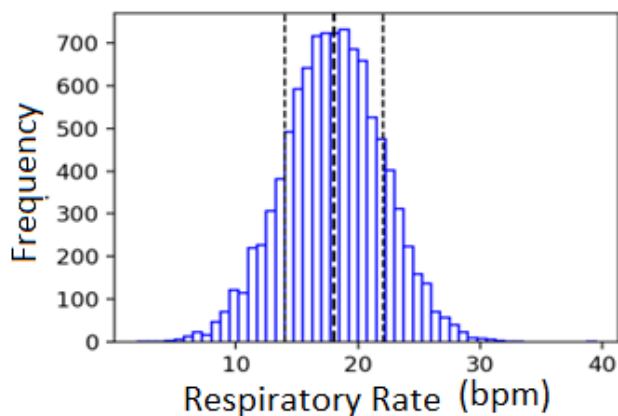**Figure 1** – Generation of random numbers for Systolic Blood Pressure – Normal or Gaussian distribution
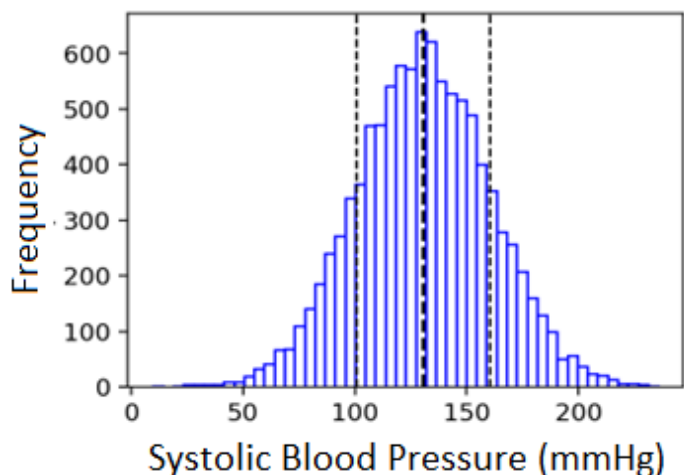
Source: Authors (2022).

Figure 2 – Generation of random numbers for Heart Rate – Normal or Gaussian distribution
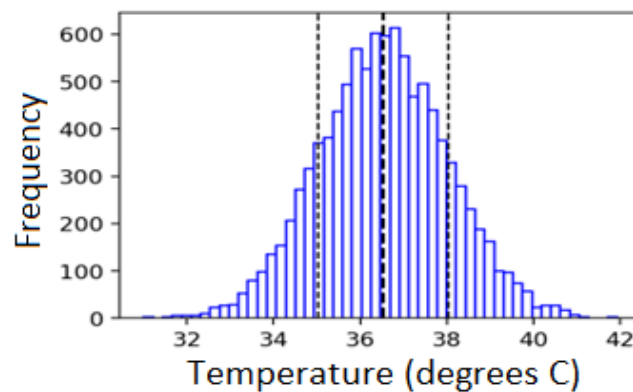

Source: Authors (2022).

Figure 3 – Generation of random numbers for Respiratory Rate – Normal or Gaussian distribution

Source: Authors (2022).

Figure 4 – Generation of random numbers for Temperature – Normal or Gaussian distribution

Source: Authors (2022).

Figure 5 – Generation of random numbers for Peripheral Oxygen Saturation – Normal or Gaussian distribution
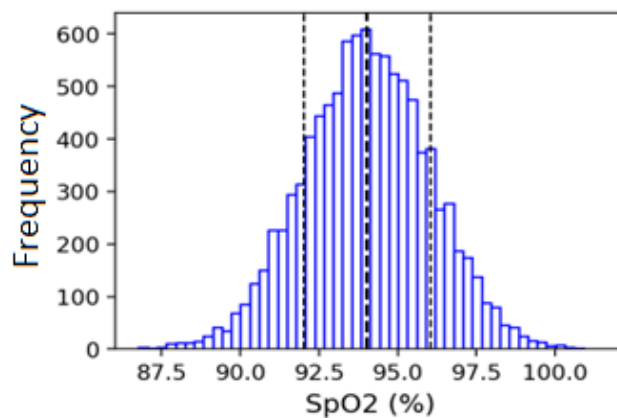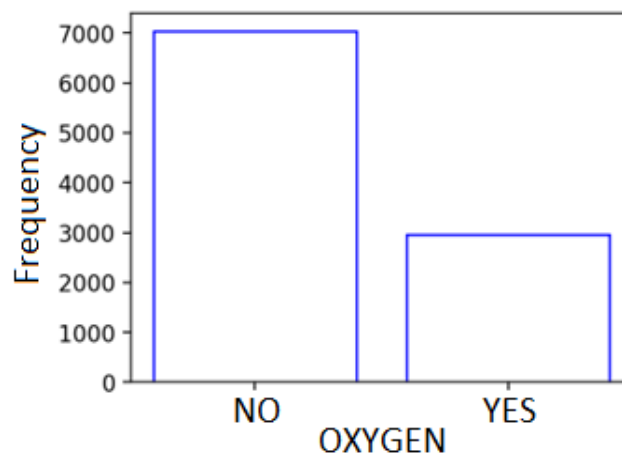

Source: Authors (2022).

Figure 6 – Generation of random numbers for Oxygen therapy – Discrete Distribution

Source: Authors (2022).

Figure 7 – Generation of random numbers for Conscious state – Discrete Distribution

For early detection of sepsis, the following parameters were considered:

- qSOFA[3]

- Patient presenting at least two or three of the criteria below is described as having a probable infection with a high probability of outcomes characteristic of sepsis (Table 1):

Table 1 – qSOFA Variables.

	0	1
Respiratory rate	< 22 bpm	≥ 22 bpm
Mental Confusion:	NO	YES
	Glasgow Coma Scale = 15	Glasgow Coma Scale < 15
Systolic blood pressure:	>100 mmHg	≤ 100 mmHg

Source: Authors (2022).

- NEWS[12]

- NEWS is characterized by the sum of the scores of the parameters below. Each of them has a score from 0 to 3. The sum of these scores gives the examiner the probability of a serious outcome in already hospitalized patients. (Table 2).

Table 2 – NEWS Variables.

	3	2	1	0	1	2	3
RR	≤ 8		9-11	12-20		21-24	≥ 25
Oximetry SpO2 (%)	≤ 91	92-93	94-95	≥ 96			
Oxygen?		Yes		No			
T	≤ 35.0		35.1-36	36.1-38	38.1-39	≥ 39,1	
SBP	≤ 90	91-100	101-110	111-219			≥ 220
HR	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Conscious				A			V, P or U

Legend: RR: Respiratory Rate; SpO2: Peripheral Oxygen Saturation; T: Temperature; SBP: Systolic Blood Pressure; HR: Heart Rate; V: responds to verbal command; P: responds to painful stimulus; U: unresponsive.
Source: Adapted from Royal College of Physicians. National Early Warning Score (NEWS) (2012).

Score

- 0-4: Low clinical risk
- 5-6: Medium clinical risk
- ≥ 7: High clinical risk

The data were stored in a database created in Excel™, exported to SPSS™ 20.0., and presented through absolute numbers and percentages, measures of central tendency and dispersion. The degree of concordance and accuracy of sepsis detection of the qSOFA score were analyzed for values greater than or equal to 2, and, in relation to the NEWS score, those greater than or equal to 7. A 95% confidence interval was considered with a statistical significance level of 5%.

RESULTS

Through a computational simulation using Monte Carlo method, a fictional 10,000 cases population was analyzed using NEWS criterion. As shown in Figures 8 and 9, it can be identified that, in 2982 cases (29.8%) the patients would score between 1 and 4, indicating that they would have minimum

risk of sepsis in the case of infection. 2743 (27.4%) scored between 5 and 6, indicating a medium risk.

Most, 4275 (42.8%), had a score of 7 or more, which indicates a high risk of the expected outcome.

.

Figure 8 – Relative frequency of NEWS score parameters
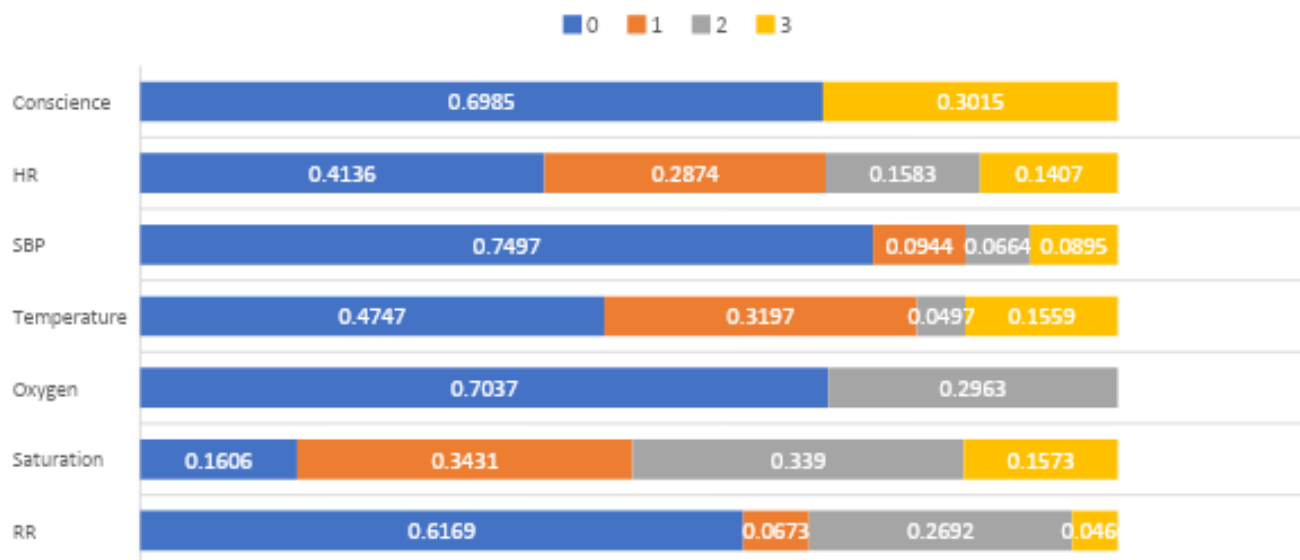
Legend: RR: Respiratory Rate; T:Temperature; SBP: Systolic Blood Pressure; HR: Heart Rate
Source: Authors (2022).

Figure 9 – Histogram of NEWS score
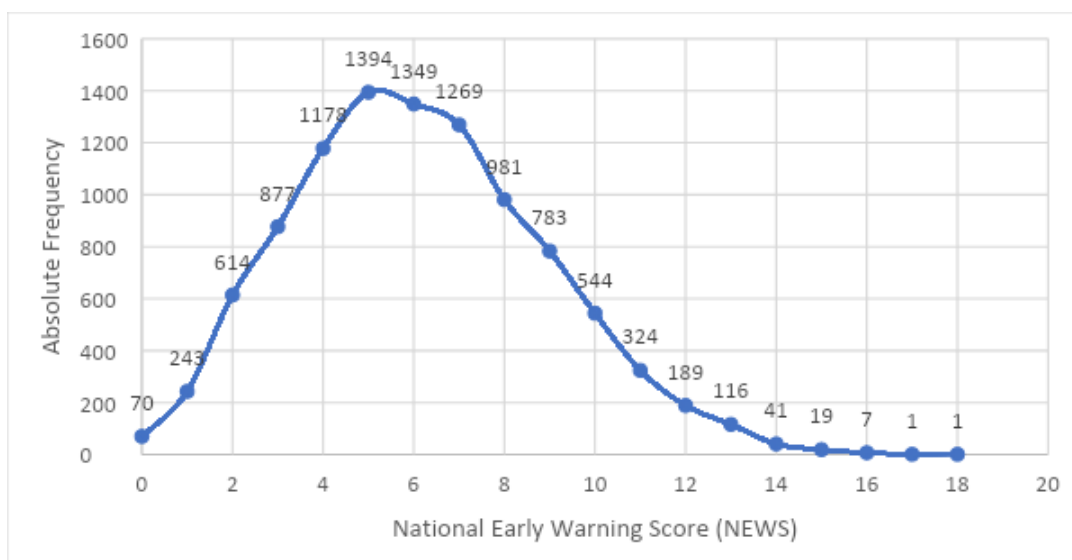
Source: Authors (2022).

In the figures 10 and 11, when the simulate cases were evaluated under the light of qSOFA criterion, different results are observed. From the established sample, only 1017 (10.2%) had more than two or three changed variables, which means that, in accordance with this criterion, would have a high risk of having sepsis. By their turn, 8983 (89.8%) scored less than two variables, not fitting the criteria to be

patients of high clinical risk and high probability of sepsis, when it is assumed that this population is in the course of infection.

Figure 10 – Relative frequency of the parameters of qSOFA score
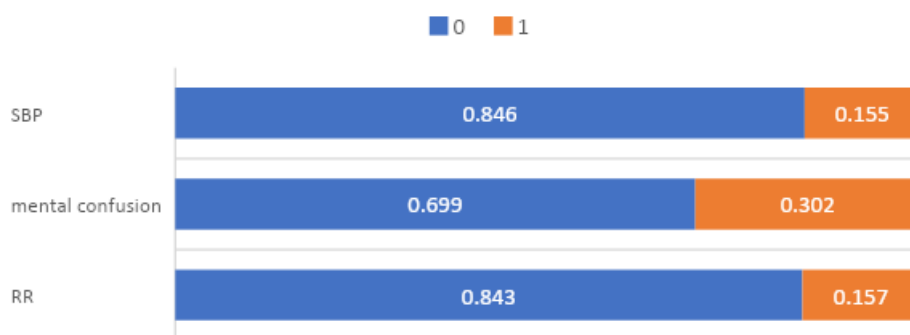
Legend: RR: Respiratory rate; SBP: Systolic blood pressure
Source: Authors (2022).

Figure 11 – Histogram of qSOFA score
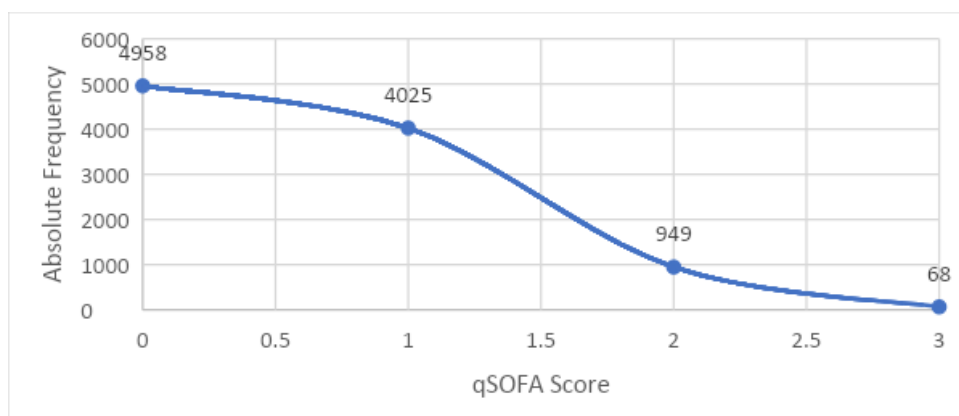
Source: Authors (2022).

When comparing qSOFA≥2 and NEWS≥7, an agreement between the two tests of 66.08% (95% CI 65.15 - 67.00) was observed. Tables 3 and 4 show the diagnostic analysis between the scores..

Table 3 - Comparing qSOFA≥2 with NEWS≥7

	NEWS≥7	NEWS<7	
qSOFA≥2	950	67	PPV 93.41%

			(IC 95% 91.72 – 94.78
qSOFA<2	3325	5658	NPV 62.99% (IC 95% 61.98 – 63.98)
	Sensitivity 22.22% (IC 95% 21.00 – 23.49)	Specificity 98.83% (IC 95% 98.52 –99.08)	

Legend: PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence Interval.
Source: Authors (2022).

Table 4 – Comparing NEWS≥7 with qSOFA≥2

	qSOFA≥2	qSOFA<2	
NEWS≥7	950	3325	PPV 22,22% (IC 95% 21.00 – 23.49)
NEWS<7	67	5658	NPV 98.83% (IC 95% 98.52 – 99.08)
	Sensitivity 93.41% (IC 95% 91.72 – 94.78)	Specificity 62.99% (IC 95% 61.98 – 63.98).	

Legend: PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence Interval.
Source: Authors (2022).

DISCUSSION

The results of the present study show that there is an agreement of 66.08% between the NEWS and qSOFA criteria, that is, in the simulated population carried out in this study, in approximately two thirds of it the criteria agree that there is a high probability of the patient having sepsis.

When comparing the two diagnosis tests, it is noted that NEWS ≥ 7 is related to a sensibility higher than qSOFA ≥ 2, the first with 93.41% and the second with only 22.22%. That is, the NEWS has a greater ability to include the population at high risk for sepsis when compared to the other criterion.

However, regarding specificity, which is the ability to identify true negatives, qSOFA has a higher percentage, with 98.83%, significantly different from NEWS, which has a specificity of around 63%.

Another analysis performed was on the predictive values. The result was PPV = 93.41% and NPV = 62.99% for qSOFA ≥2 and PPV = 22.22% and NPV = 98.83% for NEWS ≥7. When analyzing the values, it is noted that the NEWS criterion has a high rate of identifying true negatives, that is, non-ill people who were not identified as suspected sepsis but has a low rate of identifying true positives. This result is in line with a study[20] carried out at a hospital in Seattle, USA, which evaluated 880 newly transplanted people who experienced at least one suspected infection after surgery, and identified, for NEWS ≥7, a PPV value = 9.3. It is also in line with another study[21], which reached a 33.9% PPV and an 87.6% NPV.

However, when analyzing the values of qSOFA ≥2, it is noted that the present study indicates a high identification of true positives, going against the grain of the previously mentioned studies[20-21], which present PPV of 7.8% and 33.8%, respectively. And, highlighting the NVP, it is notable that the studies mentioned above concluded that the qSOFA presents a higher detection of true negative cases, with NPV of 96.4%[20] and 81.5%.[21]

qSOFA was created in 2016 through SEPSES-3 TASKFORCE3[3] with the aim of standardizing and facilitating the suspicion of sepsis, since the other criteria used, such as NEWS, required more

infrastructure, time, technical skill and, in some cases, calculation errors have already been described.[22] In this study, 6.7% of errors and 0.6% of omissions were described when the "pen and paper" method was used.[22] As a way of mitigating this error, the researchers suggested the use of technology as a way to obtain a more faithful calculation and not lose variables during this evaluation.

However, when it comes to NEWS score, its use is not only limited to patients under suspicious of infection. It is also used for all acute diseases which reach emergency, such as sepsis, as well as cardiovascular ones, lung affections, and any severe situation which may lead to death. Its use is of great importance, including: severity and mortality indicator, follow-up of the patient's clinical progression and indicator of initiation or maintenance of treatments.[12]

Several post-implementation studies of qSOFA were launched evaluating its use in practice. Most studies came to the conclusion that this criterion has several flaws, the main one being the low sensitivity in detecting possible outcomes such as sepsis and death.[20,23] As demonstrated in the present simulation, which indicated a greater inclusion of cases by NEWS≥7, when compared to qSOFA≥2, which reinforces the previously presented results.

Another study[24], which included more than 8,000 patients and evaluated the sensitivity and specificity of the qSOFA test, revealed a sensitivity of 29.7% and a specificity of 96.1%, corroborating the results of the present study already highlighted above.

With this information, it is understood the reason, when compared to qSOFA in the present study, NEWS displays a greater sensibility in the detection of suspicious of sepsis, since it was also developed thinking about encompassing other diseases in addition to this one.

In a research[20] with more than 30,000 people who arrived at the emergency room between 2008 and 2016 in the USA, with suspected infection and had one of the criteria analyzed above, it can be said that there was a convergence between the results when compared to that of the present study. According to Churpek,[20] the qSOFA≥2 test obtained a sensitivity of 53.6% regarding the sepsis outcome, while the NEWS≥7 had a greater sensitivity, reaching a value of 76.5%. And when analyzing specificity, it is observed that qSOFA was superior to NEWS, where the first presented 66.7% and the second, 52.7%.

In a 2018 study[15], which compared the NEWS and qSOFA criteria according to different outcomes, including death from sepsis, similar results were found in another study[20] and in the present study. According to it, NEWS≥7 was more useful in identifying patients with infection and sepsis (sensitivity), however, when analyzing patients without infection, qSOFA≥2 performed better, showing to be more specific.

Unlike this research, which aimed to compare the criteria through a virtually simulated population, using sepsis as the outcome, one study[15] used a sample of more than 241,000 patients through a retrospective study, and analyzed the outcome in terms of mortality. The conclusion was that NEWS, when infection is suspected, is a more accurate tool to predict death compared to qSOFA.

Another retrospective cohort study,[23] carried out in 2018, evaluated the ability of qSOFA and NEWS test on predicting mortality in patients with suspicious of sepsis, and the results, again, fit with the above-mentioned studies and the present study. The sensitivity of NEWS was 74% while the one of qSOFA was 37%, and specificities were 43% and 79%, respectively.

Other studies[15,23] reached the same conclusion regarding the predictive capacity of the tests highlighted in this study, where NEWS would be a better predictor of mortality in patients with suspected sepsis, and SEPSE-TASKFORCE3 should review its position regarding whether qSOFA is or is not the best emergency screening method. The authors support this argument through the statistical

analyzes demonstrated above, where it was identified, based on the sensitivity and specificity of both in predicting mortality, a greater gain when using the NEWS criterion as a predictor of sepsis in patients in the emergency room.[15,23]

To reach the results above described, To reach the results described above, a fictitious population of 10,000 cases was used and the Monte Carlo Simulation model was applied. This model has been used in medicine for over 60 years, with the oldest study found in Publisher MEDLINE (PUBMED) in 1950.[25]

Amongst the studies that use the Monte Carlo simulation, it can be quoted the one[26] carried out in 2017, which used this tool to predict the use of hospital beds in the case of emergency situation such as a great disaster with countless victims. In addition to this, a study[27] also carried out in 2017, used the Monte Carlo simulation to demonstrate the economic and health gains when school clinics (Student Run Clinics) were implemented in an area with delayed access to health. A 2019 study[28] used the same tool to simulate the impact on hospital costs when controlling hypotension in patients with suspected sepsis in the emergency room. All these examples justify the choice of computer simulation through the Monte Carlo Method for this study, showing that there is a significant gain when technology and science are combined in medicine.

To implement the Monte Carlo simulation within the present study, considerations were made. Amongst the positive considerations regarding the introduction of this study method, it was highlighted the greater speed to reach the expected results, not being necessary to enter the hospital environment or database. Another would be the ability to include a larger population in the study and use the same population to evaluate both criteria (NEWS and qSOFA), not needing to be in a large center to carry out a study of such importance. Also, it can be stated as an advantage in using the simulation the presence of all necessary variables to have a reliable result, unlike when using real data, where the researcher often finds it difficult to locate all the necessary information.

However, there are limitations in the use of simulation by the Monte Carlo method. Among them, the use of simulated data that may not faithfully correspond to reality. However, it is considered that this limitation has been minimized, due to the use of simulated physiological parameters within a realistic confidence interval.

CONCLUSION

The present study demonstrated, through a computational simulation using the Monte Carlo method, the concordance, and the diagnostic tests of the QSOFA and NEWS criteria, when used to assess the risk of sepsis in patients in the emergency room.

The study showed good agreement between scores and that the NEWS test is superior to qSOFA when analyzing its sensitivity, but the result is reversed when related to specificity.

This finding, therefore, when compared to current studies, corroborates their results, demonstrating that the SEPSE-3 Taskforce should review qSOFA as the method of choice to predict sepsis.

RESUMO

Introdução: Os escores de alerta precoce utilizados para sepse possuem diferentes métricas de estratificação de risco e acurácia, que podem atrasar o diagnóstico pela equipe de saúde. **Objetivo**: O estudo tem como objetivo avaliar a concordância e as diferenças entre os critérios qSOFA e NEWS na detecção precoce do risco de sepse em uma população definida através de uma simulação computacional. **Delineamento**: Foi realizada uma simulação computacional utilizando o método de Monte Carlo. Foram simulados 10.000 casos com base nas variáveis descritas pelos escores NEWS e qSOFA. **Resultados**: Após avaliação dos 10.000 casos, o qSOFA≥2 mostrou-se menos sensível (22,22% (IC 95% 21,00 – 23,49)) do que o NEWS≥7 (93.41% (IC 95% 91,72 –

94,78)). Quando se analisa a especificidade, o NEWS≥7 (62.99% (IC 95% 61,98 – 63,98)) foi inferior ao qSOFA≥2 (98,83% (IC 95% 98,52 – 99,08)). A concordância foi de 66.08% (IC 95% 65,15 - 67,00). **Implicações**: O estudo demonstrou uma boa concordância entre os escores e que o NEWS obtém superioridade ao qSOFA quando analisado a sua sensibilidade, porém o resultado se inverte quando se fala em especificidade.

DESCRITORES

Simulação por Computador; Escores de Disfunção Orgânica; Técnicas e Procedimentos Diagnósticos; Sensibilidade e Especificidade.

RESUMEN

Introducción: Los puntajes de alerta temprana utilizados para la sepsis tienen diferentes estratificaciones de riesgo y métricas de precisión, lo que puede retrasar el diagnóstico por parte del equipo de salud. **Objetivo:** El estudio tiene como objetivo evaluar la concordancia y las diferencias entre los criterios qSOFA y NEWS en la detección temprana de riesgo de sepsis en una población definida a través de una simulación por computadora. **Delineación:** Se realizó una simulación por computadora utilizando el método Monte Carlo. Se simularon 10.000 casos en base a las variables descritas por los puntajes NEWS y qSOFA. Resultados: Después de evaluar 10.000 casos, qSOFA≥2 fue menos sensible (22,22% (IC 95% 21,00 – 23,49)) que NEWS≥7 (93,41% (IC 95% 91, 72 – 94,78)). Al analizar la especificidad, NEWS≥7 (62,99% (IC 95% 61,98 – 63,98)) fue menor que qSOFA≥2 (98,83% (IC 95% 98,52 – 99,08)) . La concordancia fue del 66,08 % (IC del 95 %: 65,15 - 67,00). **Implicaciones:** El estudio mostró buena concordancia entre las puntuaciones y que NEWS es superior a qSOFA al analizar su sensibilidad, pero el resultado se invierte al hablar de especificidad.

DESCRIPTORES

Sepsis; Simulación por Computador; Puntuaciones en la Disfunción de Órganos; Técnicas y Procedimientos Diagnósticos; Sensibilidad y Especificidad.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest [Internet]. 1992 Jun [cited 2021 Nov 02];101(6):1644-55. Available from: https://doi.org/10.1378/chest.101.6.1644

2. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med [Internet]. 2003 Apr [cited 2021 Nov 02];31(4):1250-6. Available from: https://doi.org/10.1097/01.CCM.0000050454.01978.3B

3. Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA - J Am Med Assoc [Internet]. 2016 Feb [cited 2021 Nov 12];315(8):801–10. Available from: https://doi.org/10.1001/jama.2016.0287

4. Rudd Ke, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet [Internet] 2020 [cited 2022 Jun 07];395:200–11.Available from: https://doi.org/10.1016/S0140-6736(19)32989-7

5. Almeida NRC, Pontes GF, Jacob FL, Deprá JVS, Porto JPP, Lima FR, et al. Analysis of trends in sepsis mortality in Brazil and by regions from 2010 to 2019. Revista de Saúde Pública [Internet] 2022 [cited 2022 Jun 07]; 56(25):1-13. Available from: https://doi.org/10.11606/s1518-8787.2022056003789>

6. Lobo SM, Rezende E, Mendes CL, de Oliveira MC. Mortality due to sepsis in Brazil in a real scenario: The Brazilian ICUs project. Rev Bras Ter Intensiva [Internet]. 2019 [cited 2021 Nov 02];31(1):1-4. Available from: https://doi.org/10.5935/0103-507X.20190008

7. Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US adults, 2013. JAMA - J Am Med Assoc [Internet]. 2016 Dec [cited 2021 Nov 02];316(23):2547-8. Available from: https://doi.org/10.1001/jama.2016.16477

8. Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med [Internet] 2018 Dec [cited 2021 Nov 02] ;46(12):1889-1897. Available from: https://doi.org/10.1097/CCM.0000000000003342

9. Arefian H, Heublein S, Scherag A, Brunkhorst FM, Younis MZ, Moerer O, Fischer D, Hartmann M. Hospital-related cost of sepsis: A systematic review. J Infect [Internet] 2017 Feb [cited 2021 Nov 02];74(2):107-117. Available from https://doi.org/10.1016/j.jinf.2016.11.006

10. Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. Crit Care [Internet] 2018 [cited 2021 Nov 02]; 22:232. Available from: https://doi.org/10.1186/s13054-018-2157-z

11. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA - J Am Med Assoc [Internet]. 2016 Feb [cited 2021 Nov 02];315(8):762–74. Available from: https://doi.org/10.1001/jama.2016.0288

12. Royal College of Physicians (UK). National Early Warning Score (NEWS):Standardising the assessment of acute-illness severity in the NHS. London; 2012 [cited 2021 Nov 12]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

13. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation [Internet]. 2013 Apr [cited 2021 Nov 12];84(4):465-70. Available from: https://doi.org/10.1016/j.resuscitation.2012.12.016

14. Spagnolli W, Rigoni M, Torri E, Cozzio S, Vettorato E, Nollo G. Application of the National Early Warning Score (NEWS) as a stratification tool on admission in an Italian acute medical ward: A perspective study. Int J Clin Pract [Internet]. 2017 Mar [cited 2021 Nov 02];71(3-4):1-8. Available from: https://doi.org/10.1111/ijcp.12934

15. Redfern OC, Smith GB, Prytherch DR, Meredith P, Inada-Kim M, Schmidt PE. A comparison of the Quick sequential (Sepsis-related) Organ failure assessment score and the National early warning score in non-ICU patients with/without infection. Crit Care Med [Internet]. 2018 Dec [cited 2021 Nov 02];46(12):1923-33. Available from: https://doi.org/10.1097/CCM.0000000000003359

16. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Royal College of Physicians; 2017 [cited 2021 Nov 15]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

17. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. Crit Care [Internet]. 2020 Jun [cited 2021 Nov 15] ;24(1):287. Available from: https://doi.org/10.1186/s13054-020-02993-5

18. Yousefi M, Yousefi M, Fogliatto FS, Ferreira RPM, Kim JH. Simulating the behavior of patients who leave a public hospital emergency department without being seen by a physician: A cellular automaton and agent-based framework. Brazilian J Med Biol Res [Internet]. 2018 [cited 2021 Nov 02];51(3):1-10. Available from: https://doi.org/10.1590/1414-431X20176961

19. Yoriyaz H. Monte Carlo Method: principles and applications in Medical Physics. Rev Bras Física Médica [Internet]. 2009 [cited 2021 Nov 02];3(1):141-9. Available from: https://doi.org/10.29384/rbfm.2009.v3.n1.p141-149

20. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, et al. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside theintensive care unit. Am J Respir Crit Care Med [Internet]. 2017 Apr [cited 2021 Nov 02];195(7):906-11. Available from: https://doi.org/10.1164/rccm.201604-0854OC

21. Lind ML, Phipps AI, Mooney S, Liu C, Fohner A, Patel K, et al. Predictive value of three clinical criteria for sepsis (qSOFA, SIRS, and NEWS) with respect to short-term mortality in allogeneic hematopoietic cell transplant recipients with suspected infections. Clin Infect Dis [Internet]. 2021 Apr [cited 2021 Nov 02]; 72(7):1220-9. Available from: https://doi.org/10.1093/cid/ciaa214

22. Prytherch DR, Smith GB, Schmidt P, Featherstone PI, Stewart K, Knight D, et al. Calculating early warning scores-A classroom comparison of pen and paper and hand-held computer methods. Resuscitation [Internet]. 2006 Aug [cited 2021 Nov 02];70(2):173-8. Available from: https://doi.org/10.1016/j.resuscitation.2005.12.002

23. Goulden R, Hoyle MC, Monis J, Railton D, Riley V, Martin P, et al. QSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J [Internet]. 2018 Jun [cited 2021 Nov 02];35(6):345-9. Available from: https://doi.org/10.1136/emermed-2017-207120

24. Williams JM, Greenslade JH, McKenzie J V., Chu K, Brown AFT, Lipman J. Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection. Chest [Internet]. 2017 Mar [cited 2021 Nov 02];151(3):586-96. Available from: https://doi.org/10.1016/j.chest.2016.10.057

25. Rogers DWO. Fifty years of Monte Carlo simulations for medical physics. Phys Med Biol [Internet]. 2006 Jul [cited 2021 Nov 02];51(13). AVailable from: https://doi.org/10.1088/0031-9155/51/13/R17

26. Toerper MF, Kelen GD, Sauer LM, Bayram JD, Catlett C, Levin S. Hospital Surge Capacity: A Web-Based Simulation Tool for Emergency Planners. Disaster Med Public Health Prep [Internet]. 2018 Aug [cited 2021 Nov 02];12(4):513-22. Available from: https://doi.org/10.1017/dmp.2017.93

27. Arenas DJ, Lett E, Klusaritz H, Teitelman AM. A Monte Carlo simulation approach for estimating the health and economic impact of interventions provided at a student-run clinic. PLoS One [Internet]. 2017 Dec 28 [cited 2021 Nov 02];12(12):e0189718. Available from: https://doi.org/10.1371/journal.pone.0189718

28. Keuffel EL, Stevens M, Gunnarsson C, Rizzo J, Sessler DI, Maheshwari K. A Monte Carlo simulation estimating US hospital cost reductions associated with hypotension control in septic ICU patients. J Med Econ [Internet]. 2019 Apr [cited 2021 Nov 02];22(4):383-9. Available from: https://doi.org/10.1080/13696998.2019.1576695

COLLABORATIONS

MDCM: substantial contributions in articles' writing, critical review, and approval of the final version. KSK: substantial contributions in the Outlining, analysis and interpretation of the data, in the critical review and approval of the final version. **All authors agree and are responsible for the content of this version of the manuscript to be published.**

ACKNOWLEDGMENTS

Not applicable.

CONFLICTS OF INTEREST
There are no conflicts of interest to declare.