

# Suspected infection in afebrile patients

## Are they septic?

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### Abstract

We prospectively evaluated afebrile patients admitted to an emergency department (ED), with suspected infection and only tachycardia or tachypnea.

The white blood cell count (WBC) was obtained, and patients were considered septic if leukocyte count was  $>12,000 \mu\text{L}^{-1}$  or  $<4000 \mu\text{L}^{-1}$  or with  $>10\%$  of band forms. Clinical data were collected to examine whether sepsis could be predicted.

Seventy patients were included and 37 (52.86%) met sepsis criteria. Self-measured fever showed an odds ratio (OR) of 5.936 (CI95% 1.450–24.295;  $P=0.0133$ ) and increased pulse pressure (PP) showed an OR of 1.405 (CI95% 1.004–1.964;  $P=0.0471$ ) on multivariate analysis. When vital signs were included in multivariate analysis, the heart rate showed an OR of 2.112 (CI95% 1.400–3.188;  $P=0.0004$ ). Self-measured fever and mean arterial pressure  $<70$  mm Hg had high positive likelihood ratios (3.86 and 2.08, respectively). The nomogram for self-measured fever showed an increase of sepsis chance from 53% (pretest) to approximately 80% (post-test).

The recognition of self-measured fever, increased PP, and the intensity of heart rate response may improve sepsis recognition in afebrile patients with tachycardia or tachypnea. These results are important for medical assessment of sepsis in remote areas, crowded and low-resourced EDs, and low-income countries, where WBC may not be readily available.

**Abbreviations:** CBC = complete blood count, ED = emergency department, HR = heart rate, IC = confidence interval, ICU = intensive care units, LR = likelihood ratio, MAP = mean arterial pressure, OR = odds ratio,  $\text{pCO}_2$  = partial pressure of carbon dioxide, PP = pulse pressure, qSOFA = quick sepsis-related organ failure assessment, ROC = receiver operating characteristic curve, SIRS = systemic inflammatory response syndrome, RR = respiratory rate, WBC = white blood cell count.

**Keywords:** diagnosis, fever, heart rate, infection, sepsis, tachycardia

## 1. Introduction

### 1.1. Background

Sepsis, severe sepsis, and septic shock are clinical conditions with high incidence and represent important causes of death worldwide.<sup>[1–4]</sup> In Brazil, mortality rates from septic shock remains particularly high, ranging between 52% and 65%.<sup>[3,4]</sup>

Prompt sepsis recognition is crucial to adequate treatment<sup>[5–9]</sup> and to improve outcomes.<sup>[5–11]</sup> Traditionally, the systemic inflammatory response syndrome (SIRS) is defined as a host response phenomenon characterized by 2 or more of the following clinical findings: body temperature  $>38^\circ\text{C}$ , or  $<36^\circ\text{C}$ ; heart rate (HR)  $>90$  beats/min; tachypnea evidenced by respiratory rate (RR)  $>20$  breaths/min or  $\text{PaCO}_2 <32$  mm Hg; and a white blood

cell count (WBC) of  $<12,000 \mu\text{L}^{-1}$ ,  $<4,000 \mu\text{L}^{-1}$  or  $>10\%$  immature (band) forms.<sup>[12]</sup>

In the last years, SIRS criteria have been criticized as it could lack specificity.<sup>[13]</sup> In this regard, the Surviving Sepsis Campaign, since 2008, promotes the identification of organ dysfunctions as an alternative approach to sepsis diagnosis.<sup>[14,15]</sup> Therefore, a task force of sepsis experts revised the current sepsis criteria. They concluded that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. They also emphasize the importance of relying on clinical signs and symptoms for the early recognition of disease severity, by means of employing the quickSOFA (quick sepsis-related organ failure assessment) a score that comprises altered sensorium, heart rate, and respiratory rate.<sup>[16]</sup>

### 1.2. Importance

The identification of organ dysfunction relies on laboratory or invasive tests,<sup>[14,15]</sup> which is time consuming, and otherwise unpractical in crowded or resource-limited emergency departments (EDs). Furthermore, in low-income countries or limited access areas, even one of the most important and basic blood tests—the complete blood count (CBC)—may not be readily available, thus delaying sepsis diagnosis.<sup>[17]</sup>

Despite concerns regarding SIRS criteria limitations, this concept has gained widespread acceptance among researchers, clinicians, and nursing staff all over the world. In particular, SIRS criteria have proven to be a reliable tool for early identification of sepsis, for immediate treatment and consequently to reduce mortality.<sup>[5,6]</sup> Although these criteria have not been validated as a reliable method in the ED setting, they

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are still being worldwide used to diagnose sepsis in clinical practice.

In this context, sepsis diagnosis relies on SIRS criteria plus suspected infection.<sup>[18]</sup> Afebrile patients may be overlooked in this setting since fever is often considered a cardinal feature of sepsis. Although fever has been incorporated into the rules of clinical prediction of bacteremia, bloodstream infections have also been documented in the absence of fever.<sup>[19,20]</sup> Thus, early recognition of sepsis can be challenging in afebrile patients with suspected infection, presenting only tachycardia or tachypnea, since physicians may underestimate sepsis probability.

### 1.3. Goals of the investigation

We intended to investigate the presence of signs and symptoms capable of predicting sepsis, in afebrile patients accepted into an ED, with suspected infection and only tachycardia or tachypnea, thus depending on the WBC count to match SIRS criteria and sepsis diagnosis. To do so, we calculated sensitivity, specificity, likelihood ratios, and predictive values of findings. We hypothesized that the prevalence of sepsis would be high and that sepsis diagnosis could be delayed in this group, since these patients did not meet sepsis criteria immediately.

All patients included in the study had their CBC obtained. Sepsis was diagnosed by the demonstration of leukopenia ( $<4000 \mu\text{L}^{-1}$ ), leukocytosis ( $>12000 \mu\text{L}^{-1}$ ), or more than 10% of immature forms in leucocyte count.<sup>[12]</sup>

## 2. Material and method

### 2.1. Study design, setting, and population

This was a prospective observational cohort of non-consecutive adult patients, admitted to the adult ED with suspected infection, normal axillary temperature, and only 1 altered vital sign, on initial physical examination. Patients were recruited during working hours, in the morning or the afternoon, between October 2013 and February 2014. The study was performed in a crowded adult emergency department, where surgical and clinical patients are assisted, at a 403-bed tertiary urban teaching hospital in the city of Campinas, São Paulo State, Brazil.

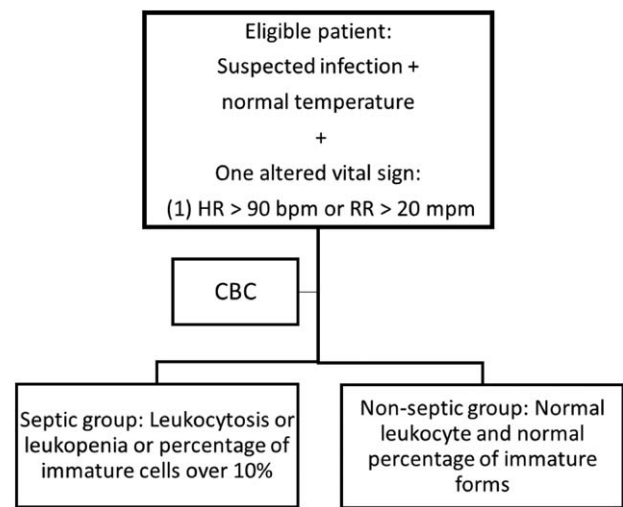
The institutional ethics committee (Faculty of Medical Science) approved the study (number: 45403/date: 06/07/2012), and informed written consent was given to eligible patients or their legal representatives.

Inclusion criteria were: (1) adult patients (aged above 18 years), with (2) suspected infection (determined in accordance with medical assessment of signs and symptoms, collected from clinical history and physical examination), (3) with normal temperature (axillary temperature above  $36^\circ\text{C}$  and less than  $38^\circ\text{C}$ ) and (4) only 1 SIRS criterion (altered vital sign), which included heart rate (HR) above 90 beats per minute OR respiratory rate (RR) above 20 movements per minute. Sepsis diagnosis was further confirmed by the chart review of all included patients.

Pre-existing conditions that were considered exclusion criteria were: (1) pregnancy or obstetric/gynecological diseases, (2) age under 18 years, (3) use of antipyretic before medical assessment (at least within 6 hours prior to medical assessment), (4) military occupation and (5) no consent to participate.

### 2.2. Study protocol, measurements, and variables

The medical history, symptoms, clinical signs, diagnostic hypothesis, and demographic data (age and gender) were



**Figure 1.** Flowchart of study methodology. Eligible patients, according to described criteria, were divided in accordance with CBC result. bpm = beats per minute, CBC = complete blood count, HR = heart rate, mpm = movements per minute, RR = respiratory rate).

obtained and registered in a specific research chart. The vital signs (arterial pressure, axillary temperature, HR and RR) from all patients were measured and registered at first medical assessment, during triage or in the emergency room. After a 60-day period, length of hospital stay and mortality rate were collected.

The suspected source of infection was determined by clinical assessment, performed by the physician on duty. The symptoms related to infection were skin or soft tissue changes, such as hyperemia and edema, or chronic ulcerations; airway symptoms as sore throat, rhinorrhea, cough, sputum, or respiration-dependent chest pain; gastrointestinal symptoms such as diarrhea or abdominal pain; genitourinary symptoms such as dysuria, pollakiuria, low back pain; or systemic symptoms such as previous measured fever, chills, and feeling faint.<sup>[21]</sup>

The altered mental status was defined as the general changes in brain function, such as confusion, amnesia, loss of alertness, loss of orientation (not cognizant of self, time or place), failure in judgment or thought, poor regulation of emotions, and disruptions in perception, psychomotor skills, and behavior.<sup>[22]</sup> Self-measured fever was defined as a self-measure of temperature (above  $38^\circ\text{C}$ ) with an axillary thermometer. Self-reported fever was defined as a report of feeling feverish and perceiving an increase in body temperature, without an objective registration. Self-reported chills were identified as a feeling of cold with shivering or shaking of the body.<sup>[23]</sup> The difficulty in maintaining the orthostatic position was defined as a report of difficulty in standing up or feeling faint.

All patients included in this research had CBC collected by the main author or by the nursing staff, according to medical request. Complete blood counts were analyzed at the clinical laboratory of the Clinical Hospital of the State University of Campinas. Patients with WBC above  $12,000 \mu\text{L}^{-1}$  or below  $4000 \mu\text{L}^{-1}$  or immature cell forms above 10% fulfilled sepsis criteria.<sup>[14]</sup> The groups (septic and nonseptic) were divided according to WBC results and consequently matching SIRS criteria (Fig. 1).

Aiming to analyze factors related to sepsis, patient data input were according to the following categories: (1) gender, (2) age, (3) self-reported fever, (4) self-measured fever, (5) self-reported

**Table 1**  
**Demographic and clinical characteristics of patients (n = 70).**

Characteristic	Nonseptic (n = 33)	Septic (n = 37)	P
Age, y, mean, $\pm$ SD	50.3 ( $\pm$ 21.97)	49.43 ( $\pm$ 21.23)	0.981
Gender, male/female, n	16/17	19/18	0.810
Leucocyte count, mean, $\pm$ SD	8210.6 ( $\pm$ 1811.3)	15494 ( $\pm$ 7532.3)	<0.0001
Vital signs			
Pulse pressure, mean, $\pm$ SD	39.58 ( $\pm$ 12.02)	47.09 ( $\pm$ 19.74)	0.104
MAP less than 70 mm Hg, n, %	3 (9.09)	7 (18.91)	0.315
Heart rate, mean, $\pm$ SD	91.94 ( $\pm$ 15.23)	104.76 ( $\pm$ 19.53)	0.012
Respiratory rate, mean, $\pm$ SD	21.73 ( $\pm$ 7.34)	20.86 ( $\pm$ 6.46)	0.743
Axillary temperature, mean, $\pm$ SD	36.61 ( $\pm$ 0.55)	36.72 ( $\pm$ 0.49)	0.256
Findings, n, %			
Self-reported fever	12 (36.36)	22 (59.45)	0.053
Self-measured fever	3 (9.09)	13 (35.13)	0.009
Self-reported chills	13 (39.39)	19 (51.35)	0.316
Altered mental status	5 (15.15)	6 (16.21)	0.902
Difficulty in maintaining orthostatic position	16 (48.48)	19 (51.35)	0.104
Suspected source of infection, n, %			0.478
Pulmonary	13 (39.39)	10 (27.03)	
Urinary	4 (12.12)	5 (13.51)	
Soft tissue	7 (21.21)	10 (27.03)	
Abdominal	6 (18.18)	8 (21.62)	
Indefinite	3 (9.09)	1 (2.70)	
Other	0 (0.00)	3 (8.11)	
Length of hospital stay, mean, $\pm$ SD	6.12 ( $\pm$ 13.49)	7.59 ( $\pm$ 12.12)	0.311
Mortality, n, %	2 (6.06)	5 (13.51)	0.264

The percentage numbers correspond to the totality of patients in each group.

MAP = mean arterial pressure, SD = standard deviation.

\* $P < 0.05$  between the 2 groups ( $\chi^2$  test, Fisher's test, and Mann-Whitney test).

chills, (6) altered mental status, (7) difficulty in maintaining orthostatic position, (8) pulse pressure (PP)—the difference between systolic and diastolic pressures, (9) mean arterial pressure (MAP), (10) HR, (11) RR, (12) axillary temperature, (13) leukocyte count, (14) suspected source of infection, (15) length of hospital stay and (16) mortality, and thus collected and compared between the 2 groups: septic *versus* non-septic patients.

### 2.3. Study size

During the 5-month period of data collection, 110 afebrile patients with suspected infection were assessed by the main author at the ED, of which 15 were excluded for lack of CBC, which had not been requested after medical assessment. Twenty-five were excluded because they presented tachycardia and tachypnea, matching sepsis diagnose immediately. No patient or family refused to participate. Thus, during the 5-month period in question, 70 afebrile patients with suspected infection and tachycardia or tachypnea were included in this study.

### 2.4. Statistical analysis

Frequency tables were made to describe sample characteristics. The categorical variables (gender, MAP less than 70 mm Hg, self-reported fever, self-measured fever, self-reported chills, altered mental status, difficulty in maintaining orthostatic position, suspected source of infection, and mortality) were described with absolute frequency values (n) and percentage (%). The numerical variables (age, leukocyte count, pulse pressure, RR, HR, axillary temperature, and length of hospital stay) were described as mean and standard deviation. The chi-square test and Fisher's exact test were used to compare categorical variables between the 2 groups.

The Mann-Whitney test was used to compare numerical variables between the 2 groups.

Univariate and multivariate logistic regression analyses were used to quantify the role of each variable on the occurrence of sepsis. The models were presented with the odds ratio (OR) and the confidence interval (CI) of 95%. The likelihood ratio (LR) test was used to calculate the positive and negative likelihood ratios, sensitivity and specificity of the findings in relation to sepsis. The level of significance for this study was 5%.

The nomograms were developed to describe the pretest and post-test probability of sepsis according to each clinical finding. Polynomial graphs were performed according to the logistic regression models to demonstrate the exponential increase in sepsis probability according to continuous variables (HR and PP).

Statistical analysis was performed using the commercially available software (the SAS System for Windows—Statistical Analysis System, version 9.2, SAS Institute Inc., 2002 to 2008, Cary, NC).

## 3. Results

During the 5-month period, 70 patients were included in the study. Thirty-seven patients (52.86%) met the criteria of sepsis. The demographic and clinical characteristics of both groups (septic and nonseptic) are presented in Table 1.

The univariate logistic regression analysis was used to identify the demographic and clinical characteristics related to sepsis. Self-measured fever showed an OR of 5.416 (95% CI 1.383–21.215;  $P = 0.0153$ ). Self-reported fever showed an OR of 2.567 (95% CI 0.977–6.746;  $P = 0.0559$ ), as demonstrated in Table 2. The vital signs (HR, RR) which are determinant criteria for sepsis diagnosis, were not included in this first logistic analysis.

**Table 2**

**Characteristics associated to sepsis (n=70) according to univariate logistic regression models.**

Characteristic	OR (CI 95%)	P
Gender	1.121 (0.439–2.868)	0.8108
Age	0.998 (0.976–1.020)	0.8643
MAP less than 70 mm Hg	2.332 (0.550–9.884)	0.2503
Pulse pressure	1.376 (0.993–1.908)	0.0555
Axillary temperature	1.533 (0.602–3.900)	0.3698
Self-reported fever	2.567 (0.977–6.746)	0.0559
Self-measured fever	5.416 (1.383–21.215)	0.0153
Self-reported chills	1.624 (0.628–4.200)	0.3173
Altered mental status	1.084 (0.298–3.945)	0.9030
Difficulty in maintaining orthostatic position	1.121 (0.439–2.868)	0.8108

CI 95% = 95% confidence interval, MAP = mean arterial pressure, OR = odds ratio.

According to multivariate logistic regression analysis, self-measured fever showed an OR of 5.936 (CI 95% 1.450–24.295;  $P=0.0133$ ). Increased values of pulse pressure showed an OR of 1.405 (CI 95% 1.004–1.964;  $P=0.0471$ ), as demonstrated in Table 3.

When HR and RR were included in logistic regression analysis, the heart rate showed in univariate analysis an OR of 1.569 (95% CI 1.130–1.178;  $P=0.0072$ ) and in multivariate analysis an OR of 2.112 (CI 95% 1.400–3.188;  $P=0.0004$ ).

The polynomial graphs performed according to the logistic regression models showed an exponential increase of sepsis probability according to the increase of heart rate (Fig. 2A) and pulse pressure (Fig. 2B).

Table 4 shows the sensitivity, specificity, positive, and negative likelihood ratios and predictive values of each clinical findings.

In Fig. 3, we observe the nomogram obtained for self-measured fever, with an increase of sepsis probability from 53% to approximately 80% (Fig. 3A). The nomogram for self-reported fever shows an increase to approximately 65% (Fig. 3B) and for MAP less than 70 mm Hg an increase to approximately 70% (Fig. 3C).

Figure 4 shows the ROC curve for the heart rate as a predictor of sepsis ( $P=0.012$ ). The cutoff of 96 indicates that the proportion of sepsis and  $HR > 96$  bpm is 62.16% (sensitivity), and the proportion of sepsis and  $HR \leq 96$  bpm is 69.70% (specificity).

#### 4. Discussion

Despite the efforts of the Surviving Sepsis Campaign in increasing the sensitivity of sepsis diagnosis,<sup>[14,15]</sup> sepsis may be underestimated in patients with normal temperature at first clinical assessment.

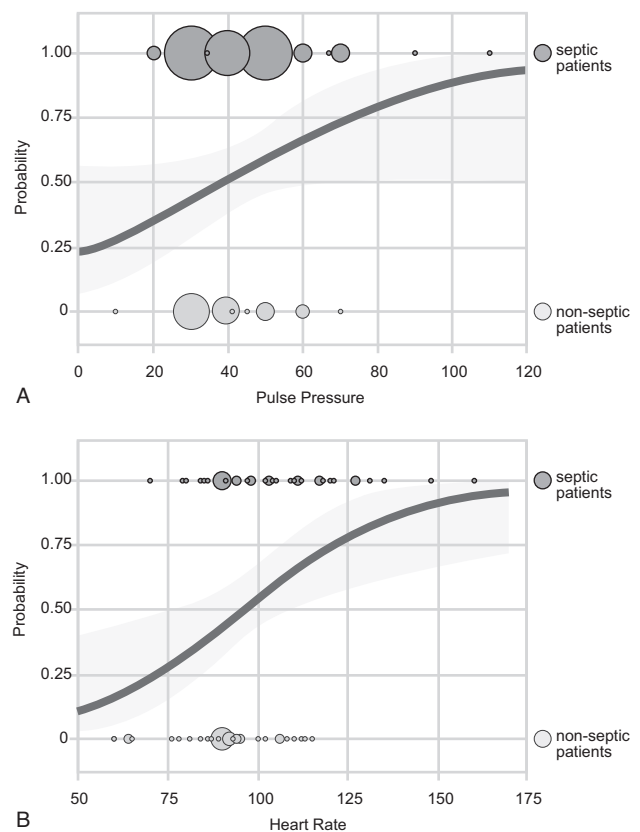
To our knowledge, this is the first study to identify clinical predictors of sepsis in patients with suspected infection with

**Table 3**

**Characteristics associated to sepsis (n=70) in multivariate logistic regression models.**

Finding	OR (CI 95%)	P
Self-measured fever	5.936 (1.450–24.295)	0.0133
Pulse pressure	1.405 (1.004–1.964)	0.0471

CI 95% = 95% confidence interval, MAP = mean arterial pressure, OR = odds ratio.



**Figure 2.** (A) Predicted probabilities for sepsis according to pulse pressure values. Graphs show exponential increases of sepsis probability according to the increase of pulse pressure. The gray area represents confidence intervals. Points in 0.00 axis represent nonseptic patient's values of pulse pressure. Points in 1.00 axis represent septic patient's values of pulse pressure. Points size enhance in accordance with the number of patients which presented specific values of pulse pressure. (B) Predicted probabilities for sepsis according to heart rate values. Graphs show exponential increases of sepsis probability according to the increase of heart rate. The gray area represents confidence intervals. Points in 0.00 axis represent nonseptic patient's values of heart rate. Points in 1.00 axis represent septic patient's values of heart rate. Sizes of points enhance in accordance with the number of patients which presented specific values of heart rate.

tachycardia or tachypnea, presenting normal axillary temperature at first clinical assessment. Worthy of consideration is that sepsis was identified in more than half (52.86%) of these patients. Furthermore, the observed mortality in this group was 13.5%. In our cohort, 25 blood cultures were collected from all patients. Thus, 16% ( $n=5$ ) of blood cultures and 8.7% ( $n=2$ ) of urine cultures were positive in septic patients. These results represent the average positivity of blood and urine cultures in our service.

In this regard, it is important to maintain suspicion of sepsis even in afebrile patients, particularly with 1 SIRS criteria at admission.

Although SIRS criteria have been criticized, it continues to be used for sepsis diagnosis in clinical practice. Sprung and colleagues have proved that SIRS criteria have prognostic importance in predicting infections, severity of disease, organ failure, and outcome. In that multicenter observational study of 198 intensive care units (ICU) in 24 European countries, 3147 new adult admissions to ICUs were analyzed. Interestingly, all infected patients had at least 2 SIRS criteria. Organ system failure and mortality increased as the number of SIRS criteria increased.<sup>[24]</sup>



**Table 4****Sensitivity, specificity, likelihood ratios, and predictive values of clinical findings among all patients (n=70).**

Finding	Sensitivity (%)	Specificity (%)	Likelihood ratio of finding		Predictive value	
			Positive	Negative	Positive	Negative
MAP less than 70 mm Hg	18.9	90.90	2.08	0.89	70.0	50.0
Self-reported fever	59.3	63.6	1.64	0.64	64.7	58.3
Self-measured fever	35.14	90.90	3.86	0.71	81.3	55.6
Self-reported chills	51.4	60.6	1.30	0.80	59.4	52.6
Altered mental status	16.2	84.8	1.07	0.99	54.5	47.5
Difficulty in maintaining orthostatic position	51.4	51.5	1.06	0.94	54.3	48.6

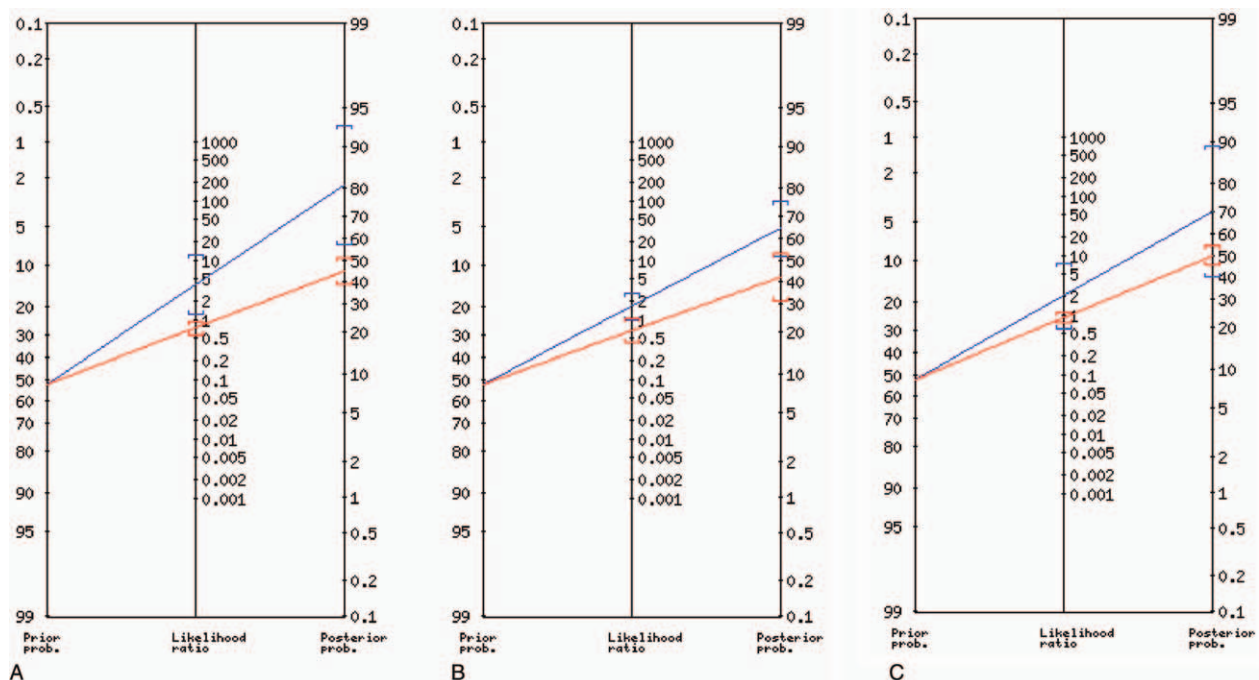
MAP = mean arterial pressure.

The alternative approach to sepsis diagnosis is the documentation of organ dysfunction, in the context of suspected infection. Despite the expected increase in the clinical sensibility, the documentation of organ dysfunction in general depends on invasive testing. However, there are plenty of clinical environments where physicians have limited access to complex laboratory analysis, such as health services in low-income countries, in remote areas, in crowded emergency departments, or even in domiciliary care. In this sense, it is important to search for clinical tools to improve our capacity to anticipate sepsis diagnosis.

In our study, the probability of sepsis increased to approximately 80% when the patient previously measured fever, as can be seen in Fig. 3A. Besides, the positive predictive value for measured fever is 81.3% (Table 4). In this context, Bossink and colleagues<sup>[25]</sup> studied the clinical host response to infection among 300 medical patients and found that peak body temperature and peak white cell count predicted infections.

Noteworthy, the self-reported fever showed a tendency to influence sepsis diagnosis. Therefore, obtaining a careful history of patients with suspected infection, in terms of the previous occurrence of fever, may be an important mean of identifying those with sepsis and its complications.

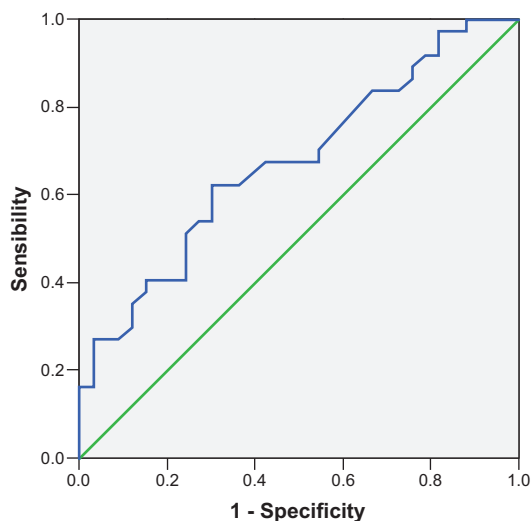
The presence of tachycardia may sign for both increased cardiac output and the occurrence of septic myocardial dysfunction.<sup>[26]</sup> A noteworthy feature of our work was that the increase in heart rate augmented exponentially the probability of sepsis. In this sense, according to the graph of HR versus sepsis, for each increase of 10 beats per minute in heart rate, the chance of sepsis doubled. Furthermore, the ROC curve for this vital sign shows that a cutoff of 96 can predict sepsis with adequate sensibility and specificity. In this regard, Kennedy and colleagues<sup>[27]</sup> showed that tachycardia was an independent factor associated with ICU transfer within 48 hours of hospital admission in patients with suspected infection. Besides, Moorman and colleagues reported heart rate as a predictor of neonatal sepsis. In this study, the characteristics of



**Figure 3.** (A) The nomogram of the relationship between self-measured fever and sepsis among all patients (n=70). The figure shows that the chance of sepsis increased from 53% in the pretest to approximately 80% in the post-test. (B) The nomogram of the relationship between self-reported fever and sepsis among all patients (n=70). The figure shows that the chance of sepsis increased from 53% in the pre-test to approximately 65% in the post-test. (C) The nomogram of the relationship between MAP less than 70 mm Hg and sepsis among all patients (n=70). The figure shows that the chance of sepsis increased from 53% in the pretest to approximately 70% in the post-test. MAP = mean arterial pressure.

Area under the curve	Standard error	p-value	95% confidence interval		Cutoff
			Lower limit	Upper limit	
0.674	0.064	0.012	0.550	0.799	96

Sensitivity: 62.16%      Specificity: 69.70%



**Figure 4.** ROC curve of heart rate. The cutoff of 96 indicates that the proportion of sepsis and HR >96 bpm is 62.16% (sensitivity), and the proportion of sepsis and HR ≤ 96 bpm is 69.70% (specificity). HR = heart rate, ROC = receiver operating characteristic curve.

heart rate and changes in white blood cell counts were significantly related to neonatal sepsis.<sup>[28]</sup>

Arterial PP is directly proportional to the stroke volume and inversely related to the compliance of the large arteries.<sup>[29]</sup> Therefore, high PP amplitudes might indicate more severe hemodynamic compromise. Even though respiratory variation of PP has been extensively studied as a marker of fluid responsiveness, in mechanically ventilated septic patients,<sup>[30,31]</sup> to date no study correlated PP with sepsis diagnosis. Likewise, according to our findings, for every increase of 10 units of pulse pressure, the chance of having sepsis increases 81%. This information may increase emergency staff awareness about the value of PP as a possible contributor of sepsis diagnosis in the emergency department, especially in afebrile patients.

In summary, our findings may contribute to improvement of early sepsis recognition, and consequently, early implementation of adequate treatment. This information is particularly important for patients admitted in the emergency setting (especially in the busiest and most resource-limited ones), but also in remote areas and in domiciliary medical care. In addition, though of rapid recognition, our findings have neither a high cost nor the need for advanced techniques.

## 5. Limitations

Our study has several limitations. Despite the assistance of the co-authors in recruiting patients (G.G), analyzing data and preparing the manuscript (T.M.S and M.A.C.F), the main author (F.S.M) solely collected data during her working hours, as there was lack of

funds and lack of staff support for data collection. However, our institution is yet beginning to perform both clinical research and semiology studies in emergency medicine. Therefore, this modality of research was the only possible in this environment. Also, we performed a convenience sample with small sample size.

In addition, our emergency department is reference for several tertiary care patients, many of them carrying risk factors for sepsis, which in turn might increase pre test probability of sepsis.

Therefore, we acknowledge the implications of these limitations in the interpretation and generalization of the results, since our findings need further validation, preferentially by means of multicenter studies.

This article represents the main author master's project results. The ethical approval occurred in 2012, although in accordance to the project schedule, data collection began in 2013 and finished in 2014, as described in the article.

## 6. Conclusions

The presence of self-measured fever, increased HR, and increased PP seem to enhance the early recognition of sepsis in afebrile patients presenting to the ED with 1 altered vital sign and suspected infection. Therefore, we suggest that the attending physician should actively search for these findings in order to improve sepsis management in this subset of patients.

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