

Mortality, intensive care treatment, and cost evaluation: Role of a polymerase chain reaction assay in patients with sepsis

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Abstract

Objective: We examined whether patients with a positive SeptiFast (SF) assay (LightCycler SeptiFast; Roche Diagnostics, Basel, Switzerland) developed higher long-term mortality, a more difficult course of treatment, and a higher antimicrobial treatment cost than patients with a negative SF assay.

Methods: We performed a post-hoc analysis of data collected in a 1-year prospective interventional study of adults with severe sepsis and septic shock. In addition to the standard treatment, an additional 5 ml of blood was obtained for an SF assay, and the antimicrobial treatment was changed according to the SF results.

Results: We included 57 patients, and the SF assay was positive (SF+) in 10 (17.5%) and negative (SF–) in 47 (82.5%) patients. A trend toward a higher 6-month, 1-year, and 2-year mortality rate was observed in the SF+ group. In the SF+ group, we observed a significantly greater need for second-line vasopressor therapy, a higher initial procalcitonin concentration, and higher maximum C-reactive protein and lactate concentrations. We found no significant differences in cost of antimicrobial treatment between the SF+ and SF– groups.

Conclusions: We observed a trend toward higher long-term mortality and a more difficult course of treatment but no difference in the cost of antimicrobial treatment.

Keywords

Sepsis, polymerase chain reaction, mortality, intensive care unit, cost, treatment

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Introduction

In recent years, several polymerase chain reaction (PCR)-based assays have become available for diagnostic work-up of patients with sepsis.^{1,2} Most studies have been performed using the SeptiFast (SF) assay

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(LightCycler SeptiFast; Roche Diagnostics, Basel, Switzerland).³⁻⁷ Initially, PCR assays were used to accelerate pathogen identification in patients with sepsis; however, in addition to pathogen identification, PCR assays can also provide supplementary information that may affect treatment strategies in patients with sepsis.⁸ Some studies have shown a correlation between positive PCR assay results and increased mortality rates, inflammatory marker levels, and disease severity scores, implying a more difficult course of treatment in patients with a positive PCR assay regardless of concordance with blood culture (BC) results⁵⁻⁷ and potentially outlining a novel, noninvasive laboratory marker of disease severity in patients with sepsis.⁸ The limiting factor preventing more widespread utilization of PCR assays is their higher cost than standard BCs.^{6,7}

This study was performed to determine whether adults with severe sepsis or septic shock who show a positive PCR assay have higher long-term mortality, a more difficult course of treatment, and a higher cost of antibiotic treatment than those with a negative PCR assay.

Methods

Study design and setting

We performed a post-hoc analysis of data collected in a prospective interventional study conducted in a 12-bed medical intensive care unit (ICU) in a tertiary hospital from September 2011 to January 2012 and from July 2012 to September 2012.⁴ The study was approved by the national ethics committee (No. 130/09/07), informed consent was obtained from all patients or their representatives, and all provisions of the Declaration of Helsinki were followed.

Before the start of the study, all attending physicians in the ICU were educated on the principles of PCR diagnostics in patients with sepsis. The decision to adjust

antimicrobial treatment based on the results of the SF assay were left to the attending physician in the ICU, and consultation with an infectious disease specialist was available at all times. Before adjusting each patient's antimicrobial therapy, additional factors were taken into consideration, including the severity of illness, general state of the patient, previous hospitalizations, previous isolates, and others. No particular protocol was used to guide the attending physicians in their decisions.

Study population

The inclusion criteria were an age of >18 years and fulfillment of criteria for severe sepsis or septic shock.⁹

Sepsis was defined as the presence of systemic inflammatory response syndrome with presumed or confirmed infection. Severe sepsis was defined as sepsis with organ dysfunction.⁹ Organ dysfunction was defined as a systolic blood pressure of <90 mmHg or mean arterial pressure of <65 mmHg, lactate concentration of >2 mmol/l, urine output of <0.5 ml/kg/h, arterial hypoxemia with a pO₂/FiO₂ ratio of <250 (or <200 if signs of pneumonia were present), creatinine concentration of >176.8 μmol/l, bilirubin concentration of >34.2 μmol/l, thrombocytopenia of <100 × 10⁹/l, or coagulopathy with an INR of >1.5 or aPTT of >60 s. Septic shock was defined as persistent hypotension requiring vasopressor support despite adequate fluid resuscitation.⁹

Standard treatment protocols were used: withdrawal of BC before antimicrobial treatment, performance of imaging studies as soon as possible to determine the source of infection and possibility of surgical treatment, initiation of antimicrobial treatment within 60 min and usual duration of 7 to 10 days, use of stress-dose steroids in patients with a blood pressure that remained unstable despite adequate fluid resuscitation

and vasopressor support, use of lung-protective ventilation (tidal volume of 6–8 ml/kg, plateau pressure of <30 cmH₂O), positive end-expiratory pressure, head of bed elevation to 30°, daily interruption or lightening of sedation, glycemic control with target blood glucose concentration of 8 to 10 mmol/l, deep vein thrombosis prophylaxis via low-molecular-weight heparins, and use of proton pump inhibitors for gastric stress ulcer prophylaxis.⁹

The goal of initial treatment was to achieve a central venous pressure of 8 to 12 mm Hg, mean arterial pressure of ≥ 65 mm Hg, urine output of ≥ 0.5 ml/kg/h, and central venous saturation (in superior vena cava) of $\geq 70\%$ or mixed venous oxygen saturation of $\geq 65\%$ within 6 h.⁹

Study intervention

In all included patients, blood samples for two pairs of standard BCs were withdrawn (2 aerobic and 2 anaerobic bottles, 40 ml of blood in all). Other microbiological samples were obtained at the discretion of the attending physician. In addition to the standard treatment and after withdrawal of blood for standard BCs, 5 ml of ethylenediaminetetraacetic acid blood was withdrawn to perform an SF assay. Blood for the SF assay was withdrawn from the same sterile peripheral vein puncture as for the BC, and if peripheral access could not be obtained, the central venous or arterial line that had been inserted upon admission was used. The SF assay was performed as soon as possible, and the results were reported to the attending physician as soon as possible. Changes to antimicrobial treatment were clinically driven according to the attending physician. The protocol has been previously described in detail.⁴

In the present post-hoc analysis, we studied the 6-month, 1-year, and 2-year mortality rates; duration of ICU and

hospital treatment; duration of mechanical ventilation; need for mechanical ventilation; need for renal replacement therapy; use and highest dose of vasopressors; initial and maximum C-reactive protein and procalcitonin levels; initial and maximum lactate levels; and cost of antimicrobial treatment. The first-choice vasopressor was noradrenalin in all patients; vasopressin was added as a second-choice vasopressor as indicated by the attending physician. The initial C-reactive protein, procalcitonin, and lactate concentrations were defined as those measured on the day that blood for the SF and BC was obtained. The maximum C-reactive protein, procalcitonin, and lactate concentrations were defined as the highest values within 7 days from the day that blood for the SF and BC was obtained. The cost of antimicrobial treatment was calculated according to prices available in the public registry of medicines.¹⁰ The cost of antimicrobial therapy was calculated as the cumulative cost of all antimicrobial therapy that a patient received in the 7 days from the day on which blood for the SF and BC was obtained. A limited evaluation of the financial impact of adding the SF assay to the cost of antimicrobial therapy was performed by considering only the material cost of the SF assay at a fixed price.

Statistical analysis

Patients with a positive SF assay (SF+) were compared with patients with a negative SF assay (SF-). Data were analyzed using SPSS for Windows package 19.0 (SPSS Inc., Chicago, IL, USA) with basic statistical methods. The data were analyzed using numbers or percentages and are expressed as median and quartile (25% and 75% percentile) or mean \pm standard deviation, depending on the distribution of normality. Fisher's exact test was used for categorical variables, the Mann-Whitney test was used for nonparametric variables, and the

unpaired t-test was used for normally distributed variables. A two-sided p-value of <0.05 was considered statistically significant. A sample size calculation was not performed because few data were available on the use of the SF assay in the clinical environment at the time of the study, and the number of cases was limited because of the cost of the assay.

Results

Sixty patients were considered for inclusion in the study. Three declined to participate, and 57 patients were therefore included (38 males, mean age of 60 ± 15 years). Ten patients (17.5%) were included in the SF+ group, and 47 patients (82.5%) were included in the SF- group. There were no differences in age, sex, or Acute Physiology and Chronic Health Evaluation II (APACHE II) score between the SF+ and SF- groups. The general demographic data are presented in Table 1.

Considering the BC results as the “gold standard,” then the SF assay achieved a sensitivity of 87.5%, specificity of 92.6%, and negative predictive value of 97.8%. Antibiotic treatment was adjusted according to the SF assay results in four (7%) patients. The time to the final results was significantly shorter with than without the SF assay (32 ± 23 h vs. 97 ± 28 h, respectively; $p < 0.0001$). The results regarding concordance between BC and the SF, the need for a change of antimicrobial treatment according to the results of the SF assay, and the time to obtaining results have been previously published in detail.⁴

Mortality analysis

The data on mortality are presented in Table 1. We observed no significant differences in the ICU, hospital, 6-month, 1-year, or 2-year mortality rates between the SF+ and SF- groups. However, the SF+ group

Table 1. General demographic and mortality data

	SF+ group	SF- group	p-value
Age, years	61 ± 16	60 ± 15	0.89
Sex, % males	60	75	0.71
APACHE II score	25 (15–32)	27 (18–33)	0.34
ICU mortality, %	40	45	0.99
Hospital mortality, %	50	53	0.99
6-month mortality, %	60	57	0.99
1-year mortality, %	80	66	0.47
2-year mortality, %	80	70	0.70

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SF+, patients with a positive SeptiFast assay; SF-, patients with a negative SeptiFast assay.

showed a trend toward a higher 6-month mortality rate (SF+, 60%; SF-, 57%; $p > 0.99$), 1-year mortality rate (SF+, 80%; SF-, 66%; $p = 0.47$), and 2-year mortality rate (SF+, 80%; SF-, 70%; $p = 0.70$).

Analysis of treatment course

Data on the course of treatment in the ICU are presented in Table 2. Both groups had a similar duration of ICU and hospital treatment, duration of mechanical ventilation, need for mechanical ventilation, and need for noradrenaline therapy. We also observed a trend toward a greater need for renal replacement therapy in the SF+ group (SF+, 30%; SF-, 17%; $p = 0.38$). We observed a significantly greater need for second-line vasopressor therapy in the SF+ group (SF+, 50%; SF-, 15%; $p = 0.025$). The maximum dose of noradrenaline was higher in the SF+ group, but the difference was not statistically significant (SF+ group: 0.38 mcg/kg/min [range, 0.14 – 0.86 mcg/kg/min] vs. SF- group: 0.30 mcg/kg/min [range, 0.20 – 0.40 mcg/kg/min]; $p = 0.55$). Both groups had similar initial C-reactive protein, lactate, and maximum procalcitonin concentrations. We observed a significantly higher initial procalcitonin concentration and significantly higher

Table 2. Data on treatment course in the intensive care unit

	SF+ group	SF- group	p-value
Duration of ICU treatment, days	11 (6–15)	13 (9–17)	0.36
Duration of hospital treatment, days	14 (11–28)	22 (11–26)	0.55
Duration of mechanical ventilation, days	11 (5–14)	12 (8–16)	0.43
Need for mechanical ventilation, %	80	75	>0.99
Need for noradrenalin therapy, %	100	89	0.57
Need for renal replacement therapy, %	30	17	0.38
Maximum dose of noradrenalin, mcg/kg/min	0.38 (0.14–0.86)	0.30 (0.20–0.40)	0.55
Need for second line vasopressor therapy, %	50	15	0.025
Initial C-reactive protein concentration, mg/l	151 ± 38	164 ± 50	0.44
Initial procalcitonin concentration, ng/ml	9.7 (7.1–21.1)	5.4 (4.5–6.9)	0.004
Initial lactate concentration, mmol/l	4.0 (2.25–5.23)	3.8 (2.6–6.0)	0.93
Maximum C-reactive protein concentration, mg/l	187 (172–227)	164 (143–184)	0.046
Maximum procalcitonin concentration, ng/ml	11.7 (7.2–21.1)	9.4 (6.9–14.4)	0.66
Maximum lactate concentration, mmol/l	5.0 (4.4–6.1)	4.0 (2.9–6.0)	0.038

SF+, patients with a positive SeptiFast assay; SF-, patients with a negative SeptiFast assay.

Values are expressed as median (25%–75% percentile), mean ± standard deviation, or percentage.

maximum C-reactive protein and lactate concentrations in the SF+ than SF- group (9.7 ng/ml [7.1–21.1 ng/ml] vs. 5.4 ng/ml [4.5–6.9 ng/ml], $p=0.004$; 187 mg/l [172–227 mg/l] vs. 164 mg/l [143–184 mg/l], $p=0.046$; and 5.0 mmol/l [4.4–6.1 mmol/l] vs. 4.0 mmol/l [2.9–6.0 mmol/l], $p=0.038$, respectively).

Cost analysis

Antimicrobial treatment was adjusted according to the results of the SF assay in four (7%) patients. In three patients, an antibiotic was added (cloxacillin for *Staphylococcus aureus*, vancomycin for *S. aureus*, and ertapenem for *Escherichia coli*). In one patient, the antibiotic was discontinued (azithromycin for *S. pneumoniae*). The antimicrobial therapy given to SF+ and BC+ patients is presented in Table 3. The cost difference for 1 week of antimicrobial therapy between the SF+ and SF- groups was not statistically significant (SF+, 322 EUR [range, 162–336 EUR] vs. SF-, 320 EUR [range, 160–380 EUR]; $p=0.86$). When the cost of the SF assay

itself was added to the calculation of costs (at a set price of 150 EUR per SF assay for material costs only),⁶ the difference remained statistically non-significant (SF+, 472 EUR [range, 308–476 EUR] vs. SF-, 470 EUR [range, 310–530 EUR]; $p=0.67$). The cost difference between 7 days of antimicrobial therapy with and without the cost of the SF assay did not reach statistical significance in the SF+ group (322 EUR [range, 162–336 EUR] vs. 472 EUR [range, 308–476 EUR]; $p=0.09$) but was statistically significant in the SF- group (320 EUR [range, 160–380 EUR] vs. 472 EUR [range, 308–476 EUR]; $p<0.001$).

Discussion

Our study revealed a trend toward higher long-term mortality, a more difficult ICU treatment course, and no significant difference in the cost of antimicrobial treatment in patients with severe sepsis or septic shock and a positive PCR assay.

Our data regarding ICU, hospital, and long-term mortality are in line with previously published studies evaluating the role

Table 3. Antimicrobial therapy for SF-negative and BC-positive patients

Patient number	SF	BC	Other sites	Previous/concomitant antibiotic therapy (dose)	Empiric antibiotic therapy (dose)	Change of therapy after SF results (dose)	Cost of 1-week antimicrobial therapy (EUR)	Outcome
1	<i>S. aureus</i>	<i>S. aureus</i>	<i>S. aureus</i> (TA)	Amoxicillin/clavulanate (1.2 g/8h)	Maxifloxacin (400 mg/24 h)	Cloxacillin (2 g/6 h)	162	Death
2	Negative	<i>S. epidermidis</i>	<i>S. epidermidis</i> (CVC tip)	Imipenem (1 g/8 h)	Imipenem (0.5 g/12 h), vancomycin (250 mg/12 h)	No change	829	Death
3	<i>E. cloacae/aerogenes</i>	Negative	<i>P. aeruginosa</i> (TA)	Ceftriaxone (2 g/24 h)	Ceftriaxone (2 g/24 h), linezolid (600 mg/12 h)	No change	818	Survival
4	<i>S. aureus</i>	<i>S. aureus</i>	<i>S. aureus</i> (TA)	Amoxicillin/clavulanate (1.2 g/8 h)	Cefepime (2 g/12 h), clindamycin (900 mg/8 h)	Vancomycin (250 mg/24 h)	315	Survival
5	<i>E. coli</i>	<i>E. coli</i>	Negative	No previous/concomitant antibiotic	Cefepime (2 g/12 h), azithromycin (500 mg/24 h)	Ertapenem (1 g/24 h)	336	Death
6	<i>S. pneumoniae</i>	Negative	<i>S. pneumoniae</i> (TA)	Amoxicillin/clavulanate acid (1.2 g/8 h)	Meropenem (1 g/8 h)	No change	322	Death
7	<i>S. pneumoniae</i>	Negative	<i>S. pneumoniae</i> (TA)	No previous/concomitant antibiotic	Ceftriaxone (2 g/24 h), azithromycin (500 mg/24 h)	No change	158	Death
8	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i> (TA)	Amoxicillin/clavulanate (1.2 g/8 h)	Ceftriaxone (2 g/24 h), azithromycin (500 mg/24 h)	Azithromycin discontinued	155	Survival
9	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i> (TA)	Amoxicillin/clavulanate (1.2 g/8 h)	Piperacillin/tazobactam (4.5 g/8 h)	No change	347	Death
10	<i>E. cloacae/aerogenes, E. coli</i>	<i>E. cloacae</i>	<i>E. cloacae</i> (TA)	Amoxicillin/clavulanate (1.2 g/8 h)	Imipenem (0.5 g/12 h), vancomycin (250 mg/12 h)	No change	334	Survival
11	<i>E. cloacae</i>	<i>E. cloacae</i>	<i>E. cloacae</i> (TA)	Piperacillin/tazobactam (4.5 g/8 h)	Meropenem (500 mg/12 h)	No change	322	Survival

SF, SeptiFast assay; BC, blood culture; TA, tracheal aspirates; CVC, central venous catheter

of PCR assays in sepsis in which the ICU mortality rate was 39.1%,⁶ 34.3%,⁷ and 29.7%,⁵ respectively, compared with 40.0% in the present study. High mortality rates in the ICU (up to 80%), during hospitalization (up to 90%), and in the long term have also been previously reported; additionally, 20% of survivors of sepsis die within 1 month of hospital discharge, 40% die within 1 year, and 80% within 5 years.^{11,12} To the best of our knowledge, this is the first study to evaluate long-term mortality in patients in whom the SF assay was used. Our data regarding the requirement for mechanical ventilation, vasopressor support, and renal replacement therapy are also in line with previously published studies.^{11,12}

A higher rate of PCR than BC positivity has been observed in several studies. Tafelski et al.¹³ performed a prospective interventional study using the SF assay in 41 patients with sepsis, and 49% of patients developed septic shock. They found positive SF results in 10 (24.4%) patients and positive BC results in 5 (12.2%) patients. In three (7.3%) patients, only the SF assay was positive while the BC and all other microbiological samples remained negative.¹³ Brealey et al.¹⁴ performed a multicentric study in patients with suspected sepsis using a new diagnostic system that enables whole-blood analysis and combines two identification techniques (PCR and electrospray ionization–mass spectrometry [ESI-MS]). In their study, 169 positive PCR/ESI-MS results (from a total of 609 samples) were BC-negative, while the negative predictive value of the assay was 97%.¹⁴

PCR assay positivity has also been associated with higher organ dysfunction scores and inflammatory marker levels in other studies. In a prospective observational study by Bloos et al.⁶ involving 142 patients with severe sepsis, 34.7% of patients had positive SF results, while 16.5% of patients had positive BC results; 21.4% of the results were concordant between the SF assay and

BC. In that study, patients with a positive SF assay had significantly higher organ dysfunction scores and a trend toward higher mortality.⁶ Similarly, in another prospective observational study by Bloos et al.⁷ involving 245 patients with suspected sepsis but involving a different whole-blood multiplex PCR assay (VYOO; SIRS-Lab GmbH, Jena, Germany), significantly higher C-reactive protein concentrations and a trend toward higher procalcitonin levels were observed in patients with a positive PCR assay, regardless of the concordance between the results of the PCR assay and standard BC.⁷ The PCR assay positivity rate was 30.0% and the BC positivity rate was 14.5% with a concordance rate of 8.7% between the two tests.⁷ Fitting et al.⁵ also used the VYOO system in 72 patients with sepsis, with a PCR positivity rate of 51.4% and BC positivity rate of 20.0%. Because of technical difficulties, they included only 72 of 300 planned patients, outlining the complexities of performing PCR assays even in academic centers.⁵ In the present study, 17.5% of the SF results and 15.7% of the BC results were positive (concordance of 11.1%).⁴ We observed a significantly higher initial procalcitonin, maximum C-reactive protein, and maximum lactate concentration in patients with a positive than negative SF assay, but no difference in the APACHE II score was found between patients with a positive and negative SF assay.⁴

The higher mortality in patients with a positive PCR assay regardless of concordance with the BC results might indicate that the presence of free microbial nucleic acids detected by the SF assay is a significant event.^{5–8} The importance of free microbial nucleic acids has also been confirmed by the presence of Toll-like receptors that recognize microbial nucleic acids on vertebrate T-lymphocytes, which are a part of the innate immune response. Certain polymorphisms in these receptors are associated with a more severe course of sepsis.¹⁵

Only whole-blood-based PCR assays were used in previous studies that evaluated the association between mortality and inflammatory markers and the results of PCR assays.⁵⁻⁷ At present, several different molecular diagnostic techniques can be used to accelerate pathogen identification in patients with sepsis.^{1,2} Higher concordance between molecular diagnostic techniques and standard BCs has been reported in assays using a positive BC result as a starting point for molecular diagnostic assays. These assays can be based on PCR analysis or other techniques (e.g., matrix-assisted laser desorption/ionization time-of-flight mass spectrometry).^{1,2} However, because a positive BC result is only a starting point, higher concordance, sensitivity, and specificity can be expected but probably little additional information can be gained (i.e., identification of free microbial nucleic acids in BC-negative samples).³ New assays are being developed, such as the PCR/ESI-MS assay, which enables rapid analysis of whole blood.¹⁴

Alterations of treatment based on the positive results of whole-blood PCR assays that can be performed apart from the modification of antimicrobial therapy may help to initiate more accurate and frequent hemodynamic monitoring. This will ensure adequate fluid and vasoactive supportive therapy,¹⁶ better source control (if possible), re-evaluation of adequate nutritional support,¹⁷ and prevention of ICU treatment-related complications.¹⁸

Bloos et al.⁷ demonstrated that cost savings can be expected with the use of a PCS assay when the daily cost of ICU treatment exceeds 717 EUR.⁷ Cost savings can be achieved through earlier initiation of appropriate antimicrobial therapy and a shorter ICU length of stay.⁷ Idevich et al.¹⁹ demonstrated that appropriate antimicrobial therapy can be delivered 26 h earlier when an SF assay is introduced to routine clinical practice. We did not observe

significant differences in the cost of 1-week antimicrobial therapy between patients with positive and negative SF assays, and the addition of the material costs of the SF assay to the 1-week cost of antimicrobial therapy resulted in significantly higher cumulative costs only in the SF- group. Great differences in the cost of antimicrobial therapy *per se* could have contributed to this (e.g., 1 day of therapy with flucloxacillin costs 29 EUR, while 1 day of therapy with meropenem costs 166 EUR).¹⁰

Study limitations

The main limitation of the present study is the small number of patients included in the study and the small number of patients with positive SF results. Additionally, we performed multiple tests to compare the attributes of two groups of patients (SF+ and SF-). Performing tests on a larger number of attributes increases the likelihood of differences between groups because of random errors, not because they are true. Second, this was a post-hoc analysis of a study originally designed and conducted, few data were available on the use of PCR assays in the routine clinical setting, and the number of included patients was limited by the availability and cost of the assay. Additionally, little data are available on the use of PCR assays in the subgroup of patients with septic shock,³ and no data are available on long-term mortality in patients with positive PCR assays. Third, the decision to institute second-line vasopressor therapy was left to the attending physician, reducing the applicability of our results. However, our patients required high doses of noradrenaline to maintain their blood pressure (median, 0.38 mcg/kg/min in the SF+ group and 0.3 mcg/kg/min in the SF- group). Administration of non-catecholamine vasopressors is recommended for patients requiring high doses of catecholamines

to maintain their blood pressure.⁹ Finally, interpretation of the SF assay results and decision to adjust the antimicrobial treatment was not protocol-driven but left to the attending physician. The attending physicians' decisions to adjust antimicrobial therapy were not based solely on the results of the SF assay but also on additional data. For example, in patients with *Escherichia coli* sepsis (Table 3, patient No. 5), the decision to add ertapenem was also based on the patient's progression of multiple organ failure after admission, frequency of previous hospitalizations, and important comorbidities (hepatic cirrhosis). Our patient died on day 2 of treatment, before the results of the BC and other microbiological samples could be obtained.

Conclusion

In patients with a positive PCR assay, we observed a trend toward a higher long-term mortality rate and more difficult ICU course of treatment; however, we found no difference in the cost of antibiotic treatment, possibly suggesting that a positive SF assay result can predict a more difficult course of treatment in patients with sepsis.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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