Specific Patterns of Postoperative Temperature Elevations Predict Blood Infection in Pediatric Burn Patients

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Using readily available temperature data, we seek to propose a scoring criteria that can facilitate accurate and immediate prediction of blood infection. The standard in diagnosing blood infection is a positive blood culture result that may take up to 3 days to process, requiring providers to make a prediction about which febrile patient is actually bacteremic. This prediction is difficult in burned children as systemic inflammation can cause fever in the absence of infection. An ability to make this prediction more accurate using readily available information would be useful. A retrospective chart review was performed for 28 pediatric patients, with a burn size 20% or greater, admitted to the burn unit between 2010 and 2014. All children had blood cultures drawn. They were divided into either infection (positive blood cultures) or control (negative blood cultures) groups. Median temperature and mean number of temperature elevations were compared between the two groups. We evaluated the predictive accuracy of using temperature elevation, pattern, and timing to predict blood infection. A significant difference was seen in the mean number of temperature elevations above 39°C. This was significant for each time stage, especially in the 0- to 24-hour post-surgery period. We found the most predictive accuracy in the 0- to 12-, 12- to 38-, and 12- to 48-hour time periods. We found a strong association between mean number of fever spikes above 39°C and blood infection, especially 12 to 24 hours after surgery. This readily available data can be useful to clinicians as they access children with burns.

The leading cause of death in pediatric burn units is sepsis. Rates of sepsis-related mortality for burn patients is 50 to 85% in adults and 55% in children.¹ Treating sepsis is the most expensive condition in U.S. hospitals at \$23.7 billion in 2013.² One of the primary reasons for this high cost is the infection is often identified during the late stages of treatment.³ Patient survival decreases by 7.6% for each passing hour of delayed antibiotic treatment of patients with sepsis.⁴ Early recognition of the signs of blood infection is the key to improving survival and reducing financial cost.⁵

Positive culture tests, though effective in diagnosing infection, are not suitable as the only indication. The waiting period for culture results is approximately 3 days. Numerous biomarkers, such as procalcitonin, C-reactive protein, tumor necrosis factor- α , interleukin-6, and interleukin-10, have been investigated as timely infection indicators.^{6,7} However, the

predictive value of these biomarkers require further research until they are implemented routinely in clinical care.⁸⁻¹³ These biomarkers are not currently used in many clinical practices, as they are often elevated in the absence of infection because of the systemic inflammation and nutritional status following the burn injury. Motivated by this need for finding early indicators of infection, this article examines the utility of using dynamic temperature trends to predict infection.

METHODS

A retrospective chart review was completed for a random sample of 50 pediatric patients admitted to the pediatric burn specialty unit between 2010 and 2014. Patients included in this sample had a TBSA burn of at least 20%. Patients who had either incomplete temperature data, no excisional grafting surgical procedure, or no blood culture drawn within 24 hours of the excisional surgery were removed from the sample. Due to this criteria, 22 patients were removed from the sample. A total of 28 patients comprised the final patient sample.

All surgical cases included in this study had a blood culture drawn within 24 hours of their surgical procedure. We divided the surgical case sample into two groups based on the culture results: The infection group included surgical cases which developed a positive blood culture result. The control group included surgical cases that had a negative culture.

Whenever available, blood cultures were drawn from central venous lines. Of the 36 surgical cases, 28 cases were confirmed to have a blood culture drawn from their central venous line. This included 15 cases in the infection group and 13 cases in

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the control group. One case in the control group was confirmed to have a blood culture drawn peripherally. We were unable to confirm the blood draw method from the remaining cases due to limited documentation in the medical record.

Statistical Analysis

Data preprocessing, including identification of typos and other errors, was performed using Mathwork's MATLAB software (Natick, MA). Subsequent statistical analyses were performed using Microsoft Excel (Redmond, WA), specifically the Analysis ToolPak Add In, for ease of comparison. Groups were compared using analysis of variance for group differences. For individual comparisons, first the *F*-test was used to determine whether there were equal or unequal variances, followed by an uncorrected Student's two-tailed *t*-test. Sidak method was employed to correct for multiple comparisons, which controls for the Type 1 error rate.¹⁴ We relied on the Student's *t*-test as a marker of whether to reject or fail to reject the null hypothesis. Our standard for statistical significance was defined as a *P* value below .05.

Comparisons

An initial analysis evaluated differences between the infection and control groups. Variables included were mean age, mean TBSA, mean percentage of third-degree burn, mean days on ventilation, mean length of stay in the intensive care unit (ICU), and mean overall length of stay.

Subsequent analyses assessed differences between groups at four different time frames: 0 to 6, 0 to 12, 0 to 24, and 0 to 72 hours post-surgery. The start of the surgical procedure was time 0 for the 72-hour study time period. The vast majority of temperature data in our sample was via rectal measurement. Rectal temperature measurement is generally considered to be the most accurate method for use in the pediatric ICU. Other methods of temperature measurement in our sample included axillary, oral, and temporal. Median temperature was compared between the infection and control groups across each time frame to identify time frames where differences were statistically significant. The next test performed compared mean number of fever spikes between groups within each time frame. Three different definitions of fever spikes were used: temperature above 38, 38.5, and 39°C.

Predictive accuracy was tested using the presence of fever spikes as an indication of blood infection. We tested three different criteria: one or more fever spikes above 39°C, two or more fever spikes above 39°C, and three or more fever spikes above 39°C. If our criteria were satisfied, blood infection was predicted as positive. If not, blood infection was predicted as negative. Time periods tested were as follows: 0- to 12-, 0- to 24-, 0- to 48-, 6- to 30-, 12- to 24-, 12- to 36-, 12- to 48-, 24- to 48-, and 0- to 72-hour post-surgery time frames. A number of predictive metrics tested for statistical value: true positive rate (sensitivity), true negative rate (specificity), positive predictive value (precision), negative predictive value, false positive rate, false negative rate, false discovery rate, accuracy, F1 score, informedness, markedness, and Matthews correlation coefficient (MCC). We used the MCC to determine the degree of agreement between our predictive formulas and the reality of data obtained.

A value of 1 indicates perfect agreement of our predictions and reality. A value of zero indicates a random correlation between our predictions and reality. A value of -1 indicates that the predictive formula consistently predicts the opposite of reality.

RESULTS

Matching

Thirty-six surgical cases were analyzed, 18 surgical cases in each group. The infection group was comprised of 15 patients. The control group was comprised 13 patients. There was no overlap of patients between both groups. The Student's *t*-test did not indicate statistically significant differences between the groups in age (*P* = .26), TBSA (*P* = .10), percentage of third-degree burn (*P* = .30), days of mechanical ventilation (*P* = .06), days in the ICU (*P* = .19), and total length of stay (*P* = .99; Table 1).

The infection group had an average age of 8.4 (SD = 5.8) years, an average burn size of 55.4 (SD = 18.6)%, an average full thickness burn of 48.4 (SD = 19.1)%, 47% had an inhalation injury, an average of 12.5 (SD = 11.5) days on ventilation, an average of 38.8 (SD = 18.2) days in the ICU, and an average length of stay of 63.3 (SD = 31.1). The control group had an average age of 6.1 (SD = 5.3) years, an average burn size of 45.8 (SD = 10.8)%, an average full thickness burn of 41.9 (SD = 11.9)%, 30% had an inhalation injury, an average of 5.9 (SD = 4.7) days on ventilation, an average of 30.4 (SD = 15.0) days in the ICU, and an average length of stay of 63.1 (SD = 46.0).

Median Temperature

Median temperatures were compared between the two groups to test whether median temperature could predict the presence of blood infection (Table 2). In each time frame, the infection group exhibited a higher median temperature than the control group. The Student's *t*-test was statistically significant in the 0- to 12-hour post-surgery (*P* = .03), 0- to 24-hour post-surgery (*P* = .011), and 0- to 72-hour post-surgery (*P* = .012) time frames. However, the difference in median temperature between the infection and control groups was small (0.5°C). Therefore, we do not see this as an independent practical predictor of infection.

Fever Spikes

We next evaluated if number of temperature elevations was predictive of infection. Fever spikes above 38°C were compared using a Student's *t*-test between the infection and control groups across each time frame (Table 3). The only statistical significance was found in the 0- to 72-hour post-surgery time frame (*P* ≤ .001). Fever spikes over 38.5°C showed statistical significance in the 0- to 12-hour post-surgery (*P* = .021), 0- to 24-hour post-surgery (*P* = .54), and 0- to 72-hour post-surgery (*P* = .001) time frames (Table 4). Fever spikes above 39°C showed statistical significance in each time frame tested, as early as 6 hours.

Out of the 36 surgical cases sampled, seven patients in the control group did not exhibit a temperature greater than 39°C. These seven patients contributed 14 surgical cases to

Table 1. Matching between infection and control groups

Study Group	Blood Culture Results	Patients	Mean Age (<i>P</i> = .26)	Inhalation Injury	Mean TBSA (<i>P</i> = .10)	Mean Third Degree (<i>P</i> = .30)	Mean Vent Days (<i>P</i> = .06)	Mean ICU Days (<i>P</i> = .19)	Mean LOS Days (<i>P</i> = .99)
Infection	Positive	15	8.4 ± 5.8	47% (7/15)	55.4 ± 18.6%	48.4 ± 19.1%	12.5 ± 11.5	38.8 ± 18.2	63.3 ± 31.1
Control	Negative	13	6.1 ± 5.3	30% (4/13)	45.8 ± 10.8%	41.9 ± 11.9%	5.9 ± 4.7	30.4 ± 15.0	63.1 ± 46.0

ICU, intensive care unit; LOS, length of stay; Vent, ventilation.

Table 2. Comparison of median temperature between infection and control groups

Study Group	T = 0–6 Hours Post-surgery				T = 0 to 12 Hours Post-surgery				T = 0 to 24 Hours Post-surgery				T = 0 to 72 Hours Post-surgery			
	Med Temp (°C)		F-Test		Med Temp (°C)		F-Test		Med Temp (°C)		F-Test		Med Temp (°C)		F-Test	
	Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)	
Infection	18	38.2	0.5	0.093	18	38.2	0.3	0.03	18	38.3	0.832	0.011*	18	38.1	0.1	0.012
Control	18	37.8			18	37.8			18	37.8			18	37.9		

Med Temp, median temperature.

*Sidak-corrected statistical significance using Student's t-test.

Table 3. Comparison of fever spikes over 38°C between infection and control groups

Study Group	T = 0 to 6 Hours Post-surgery				T = 0 to 12 Hours Post-surgery				T = 0 to 24 Hours Post-surgery				T = 0 to 72 Hours Post-surgery			
	Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test	
	Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)	
Infection	18	1.5	0.12	0.200	18	2.2	0.1	0.21	18	3.3	0.64	0.096	18	9.3	0.26	3.24 × 10 ⁻⁷ *
Control	18	1.1			18	1.7			18	2.6			18	4.7		

*Sidak-corrected statistical significance using Student's t-test.

Table 4. Comparison of fever spikes over 38.5°C between infection and control groups

Study Group	T = 0 to 6 Hours Post-surgery				T = 0 to 12 Hours Post-surgery				T = 0 to 24 Hours Post-surgery				T = 0 to 72 Hours Post-surgery			
	Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test		Mean Fever Spikes		F-Test	
	Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)		Surgical Cases		T-Test (<i>P</i> Value)	
Infection	18	1.3	0.38	0.13	18	1.6	0.82	0.021*	18	2.9	0.54	0.038*	18	6.7	0.43	0.001*
Control	18	0.9			18	0.9			18	1.8			18	4.1		

*Sidak-corrected statistical significance using Student's t-test.

our sample. Only one patient who contributed one surgical case in the infection group did not have a temperature greater than 39°C within the 72-hour study time period.

Out of the 36 surgical cases sampled, two patients in the infection group which both contributed one surgical case had a hypothermic temperature during the 72-hour study time period. Hypothermic temperature was defined by a temperature below 35°C.

Figure 1 depicts the temperature charts for two representative surgical cases from the summary data presented in Table 4. In the infection group, the spike points are marked and would be easy to detect by patient care staff at time of measurement (Figure 1A). The sample patient case exhibits a high degree of fluctuation in temperature throughout the 72-hour post-surgery time period. The patient exceeds the 39°C threshold five times within the 72 hour period. Whereas the sample patient from the control group exhibits more stability in the temperature time series (Figure 1B). The 39°C threshold only exceeds once at the 20th hour post-excisional surgery.

Predictive Analysis

The number of fever spikes above 39°C appeared to be the most readily detectable difference and a marker that could be used as early as 6 hours. We therefore proceeded to evaluate this metric as a predictive marker of blood infections. The test chosen, to be readily adoptable clinically, was the number of fever measurements over 39°C in a selected period of observation; the test was considered across multiple time frames, and different number of “spikes” was also considered (Table 5).

Using one or more temperature readings above 39°C as the predictive criteria, we found the strongest predictive value in the 0- to 12-hour post-surgery time frame with an MCC of 0.62 (Table 6). This included a sensitivity of 72% and specificity of 89%. The highest sensitivity using this criteria was 94% in the 0- to 48-hour post-surgery time frame; however, the specificity was only 44%.

Using two or more fever spikes as the predictive criteria, we found the strongest predictive value in the 12- to 36- and 12- to 48-hour post-surgery time frames with a MCC of 0.73 (Table 7). This was the highest MCC found across all criteria and time frames tested. For the 12- to 36-hour time frame,

the sensitivity was 78% and the specificity is 94%. For the 12- to 48-hour time frame, the sensitivity was 94% and the specificity was 78%. The MCC of the 0- to 12-hour time frame remained at 0.62.

Last, we used three or more fever spikes as the predictive criteria. This criteria provided the weakest predictive results. The highest MCC found was 0.56 in the 0- to 72-hour post-surgery time frame. Using this criteria, we had high specificity and low sensitivity across the time frames (Table 8).

Patient Mortality

Two patients in the infection group died in the hospital. One patient contributed three surgical cases to the infection group sample. This patient died outside of the three 72-hour study time periods. The other patient in the infection group expired at the 70.6th hour of the study time period.

DISCUSSION

Our results suggest that the number of fever spikes over 39°C predict positive blood cultures within the 48 hours following excisional surgery in burn patients. This data may support empiric antibiotic coverage while awaiting definitive culture results.

Thirty-one of the 36 surgical cases received antipyretic medication, specifically acetaminophen and ibuprofen, within 24 hours of their surgery start time. For one surgical case in the infection group the patient did not receive antipyretic medication as they were hypothermic. Due to limited access to medical records dating back prior to 2011, we were unable to confirm whether four patients were on antipyretic medication during the study time period.

As this is a retrospective study, it was difficult to decipher from the medical record whether antipyretic medications were administered by clinicians for the purpose of pain control, reducing fever, or both of these purposes. As a standard practice at our facility, clinical staff administer antipyretic medications for the purpose of reducing fever and not directly for pain control.

It is likely that instances of fever spikes are affected by the use of antipyretic medications, given the drug’s mechanism

Figure 1. Temperature trendlines of sample patients from infection and control groups. (A) Temperature trendline of infection group patient. (B) Temperature trendline of control group patient.

Table 5. Comparison of fever spikes over 39°C between infection and control groups

Study Group	Surgical Cases	T = 0 to 6 Hours Post-surgery			T = 0 to 12 Hours Post-surgery			T = 0 to 24 Hours Post-surgery			T = 0 to 72 Hours Post-surgery		
		Mean Fever Spikes	F-Test	T-Test (P Value)	Mean Fever Spikes	F-Test	T-Test (P Value)	Mean Fever Spikes	F-Test	T-Test (P Value)	Mean Fever Spikes	F-Test	T-Test (P Value)
Infection	18	0.8	0.02	0.007*	1.1	0.1	0.0047*	1.7	0.24	0.003*	1.7	0.46	0.037*
Control	18	0.2			0.3			0.6			1		

*Sidak-corrected statistical significance using Student's *t*-test.**Table 6.** Prediction accuracy analysis for using one or more temperature readings above 39°C as a marker of infection in blood

Predictive Metric	Time Frame in Hours								
	0 to 12	0 to 24	0 to 48	6 to 30	12 to 24	12 to 36	12 to 48	24 to 48	0 to 72
True positive rate (sensitivity)	72%	83%	94%	67%	44%	67%	89%	78%	94%
True negative rate (specificity)	89%	67%	44%	72%	78%	61%	61%	56%	39%
Positive predictive value (precision)	87%	71%	63%	71%	67%	63%	70%	64%	61%
Negative predictive value	76%	80%	89%	68%	58%	65%	85%	71%	88%
False positive rate	11%	33%	56%	28%	22%	39%	39%	44%	61%
False negative rate	28%	17%	6%	33%	56%	33%	11%	22%	6%
False discovery rate	13%	29%	37%	29%	33%	37%	30%	36%	39%
Accuracy	81%	75%	69%	69%	61%	64%	75%	67%	75%
F1 Score	79%	77%	76%	69%	53%	65%	78%	70%	74%
Informedness	0.61	0.50	0.39	0.39	0.22	0.28	0.50	0.33	0.33
Markedness	0.63	0.51	0.52	0.39	0.25	0.28	0.54	0.35	0.48
Matthews correlation coefficient	0.62	0.51	0.45	0.39	0.24	0.28	0.52	0.34	0.51

Table 7. Prediction accuracy analysis for using two or more temperature readings above 39°C as a marker of infection in blood

Predictive Metric	Time Frame in Hours								
	0 to 12	0 to 24	0 to 48	6 to 30	12 to 24	12 to 36	12 to 48	24 to 48	0 to 72
True positive rate (sensitivity)	56%	56%	22%	56%	50%	78%	94%	67%	89%
True negative rate (specificity)	100%	89%	94%	83%	78%	94%	78%	83%	61%
Positive predictive value (precision)	100%	83%	80%	77%	69%	93%	81%	80%	70%
Negative predictive value	69%	67%	55%	65%	61%	81%	93%	71%	85%
False positive rate	0%	11%	6%	17%	22%	6%	22%	17%	39%
False negative rate	44%	44%	78%	44%	50%	22%	6%	33%	11%
False discovery rate	0%	17%	20%	23%	31%	7%	19%	20%	30%
Accuracy	78%	72%	58%	69%	64%	86%	86%	75%	75%
F1 score	71%	67%	35%	65%	58%	85%	87%	73%	78%
Informedness	0.56	0.44	0.17	0.39	0.28	0.72	0.72	0.50	0.50
Markedness	0.69	0.50	0.35	0.42	0.30	0.74	0.74	0.51	0.54
Matthews correlation coefficient	0.62	0.47	0.24	0.40	0.29	0.73	0.73	0.51	0.52

Table 8. Prediction accuracy analysis for using three or more temperature readings above 39°C as a marker of infection in blood

Predictive Metric	Time Frame in Hours								
	0 to 12	0 to 24	0 to 48	6 to 30	12 to 24	12 to 36	12 to 48	24 to 48	0 to 72
True positive rate (sensitivity)	33%	39%	11%	28%	33%	50%	67%	33%	78%
True negative rate (specificity)	100%	94%	94%	89%	89%	94%	83%	89%	78%
Positive predictive value (precision)	100%	94%	94%	89%	89%	94%	83%	89%	78%
Negative predictive value	100%	88%	67%	71%	75%	90%	80%	75%	78%
False positive rate	0%	6%	6%	11%	11%	6%	17%	11%	22%
False negative rate	67%	61%	89%	72%	67%	50%	33%	67%	22%
False discovery rate	0%	13%	33%	29%	25%	10%	20%	25%	22%
Accuracy	67%	67%	53%	58%	61%	72%	75%	61%	78%
F1 score	50%	54%	19%	40%	46%	64%	73%	46%	78%
Informedness	0.33	0.33	0.06	0.17	0.22	0.44	0.50	0.22	0.56
Markedness	0.60	0.48	0.18	0.27	0.32	0.55	0.51	0.32	0.56
Matthews correlation coefficient	0.45	0.40	0.10	0.21	0.27	0.50	0.51	0.27	0.56

to reduce fever. However, the majority of patients in both groups were exposed to these medications. Therefore, we do not believe the use of antipyretic medications affects the significance of our results. Rather our results show that even in the presence of antipyretic medications, fever spikes patterns may be utilized to identify infection.

Twenty-five of the 36 surgical cases were confirmed to be on antibiotics during the study time period. Thirteen of these cases were in the infection group. Twelve of these cases were in the control group. One patient in the control group was confirmed to not be on antibiotics. Due to limited access to medical records dating back prior to 2011, we were unable to confirm whether ten patients were on antibiotics medication during the study time period.

Other sepsis scoring systems have been developed to predict the likelihood of bacteremia. By using our results alongside these scoring systems, the accurate and timely indication of blood infection may be improved. The Quick Sequential Organ Failure Assessment assigns +1 to a patient with any of the following: an altered mental status, respiratory rate over 22 breaths per minute, or a systolic blood pressure under 100 mm Hg.¹⁵

The presence of two or more indicates likelihood of sepsis. Unfortunately, all of these findings are consistent with normal post-burn physiology. The systemic inflammatory response syndrome criteria assigns +1 for any of the following: temperature outside of the 36 to 38°C range, heart rate over 90 beats per minute, respiratory rate over 20 breaths per minute, white blood count of outside of the 4000 to 12,000/mm³ range.¹⁶ The American Burn Association (ABA) diagnostic criteria proposes that the presence of three or more of the following indicates sepsis: temperature of >39°C or <36.5°C, progressive tachycardia, progressive tachypnea, thrombocytopenia, hyperglycemia (without preexisting diabetes mellitus), and inability to continue enteral feedings over 24 hours.¹⁷ The Modified Early Warning System (MEWS) evaluates respiratory rate, heart rate, systolic blood pressure, conscious level (AVPU), temperature, and hourly urine.¹⁸ More statistical weight is added for more extreme values. For example, a temperature in the 38.1 to 38.5°C range receives a value of 1. Whereas a temperature in excess of 38.6°C receives a value of 2.

The scoring criteria noted above can be readily modified to incorporate our findings. The Quick Sequential Organ Failure

Assessment criteria currently does not evaluate temperature. As temperature readings of patients can be quickly obtained, adding the metric of a temperature over 39°C can improve how clinicians assess susceptibility to infection.

For the criteria that already incorporates temperature trends, we suggest rather than focusing on the absolute values (e.g. does the temperature exceed 39°C), assign more weight for repeated temperature extremes (e.g. how many measurements exceed 39°C). The scoring criteria noted above can be readily modified to specifically look for the number of fever spikes over 39°C. This criteria may also be further enhanced by adding more statistical weight to fever spikes identified during the critical time periods of 0 to 12, 12 to 36, and/or 12 to 48 hours post-surgery. This approach can be a valuable and new way to interrogate the available data.

As a result of our findings we propose a simple scoring system called the Boston Spike Test to assess the likelihood of blood infection following surgery. This test is innovative in that it considers the number of fever spikes above 39°C as well as focuses on the critical time periods following surgery. If a temperature above 39°C occurs in the first 12 hours following surgery assign a value of 1. For every temperature spike above 39°C in 12 to 48 hours following surgery assign a value of 1. A cumulative value equal to or greater than 2 satisfies the Boston Spike Test criteria for susceptibility to infection. This simple test can be quickly implemented in burn units. We are currently developing a clinical study to prospectively evaluate the predictability of the Boston Spike Test.

We also believe that there is significant clinical value in incorporating the Boston Spike Test into existing and future comprehensive monitoring systems. A variety of hospital systems have implemented data monitoring software applications in clinical units such as the Penn E-Lert eICU and the Philips eICU.^{18,19,20} These systems issue alerts to designated intensivists who are monitoring patients from a central location and could be programed to alert for such temperature fluctuations.

Limitations

Our study design does not incorporate the culture results of other etiologies of fevers such as pneumonia, urinary tract infection, or wound infection. We would expect that the Boston Spike Test would adequately respond to these fevers etiologies; however, this would need to be verified in a follow-up study. In addition, follow-up studies would benefit from evaluating a longer study time period of temperature data as well as repeated pan cultures for each patient.

Fevers following surgery may be caused by atelectasis rather than infection. However, fevers induced by atelectasis are typically low grade (37 to 38°C). We believe this is a reason why our results were strongest when using a fever spike definition of greater than 39°C. In addition, both the infection and control groups had an equal likelihood of developing atelectasis, as they were both exposed to general anesthesia at time 0. Given this equal likelihood, we do not believe our results are affected significantly by atelectasis.

Our statistical analyses do not account for confounding with other clinical variables. For example, an elevated temperature can be heavily correlated with a drop in systolic blood pressure. Multivariate regression analyses or dynamic modeling is currently under consideration in future studies. These models would likely improve accuracy, in particular the sensitivity of detection attained by the simple approach here, and may lead to formulae that are simple to apply but involve multiple observed variables. Although we considered only blood culture results in our analyses, pan cultures and x-rays will be considered in future studies. Moreover, this is a small and retrospective study, and the results need to be tested in a blinded and randomized fashion. A larger follow-up clinical prospective study with such characteristics is currently in development.

Another avenue of exploration is incorporating biomarker data. In future studies, we plan to collect blood samples to evaluate the clinical benefit of biomarkers in providing early identification of systemic infection such as procalcitonin, C-reactive protein, tumor necrosis factor- α , interleukin-6, and interleukin-10.

In addition, our analyses make the assumption that immunosuppressed patients can still develop signs of fever. This is not always the case as immunocompromised patients may not have the appropriate cytokine cascade to raise their internal temperature.²¹

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