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Costs and Consequences of a Novel Emergency Department Sepsis Diagnostic Test: The IntelliSep Index

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OBJECTIVES: Sepsis causes 270,000 deaths and costs $38 billion annually in the United States. Most cases of sepsis present in the emergency department (ED), where rapid diagnosis remains challenging. The IntelliSep Index (ISI) is a novel diagnostic test that analyzes characteristics of WBC structure and provides a reliable early signal for sepsis. This study performs a cost-consequence analysis of the ISI relative to procalcitonin for early sepsis diagnosis in the ED.

PERSPECTIVE: U.S. healthcare system.

SETTING: Community hospital ED.

METHODS: A decision tree analysis was performed comparing ISI with procalcitonin. Model parameters included prevalence of sepsis, sensitivity and specificity of diagnostic tests (both ISI and procalcitonin), costs of hospitalization, and mortality rate stratified by diagnostic test result. Mortality and prevalence of sepsis were estimated from best available literature. Costs were estimated based on an analysis of a large, national discharge dataset, and adjusted to 2018 U.S. dollars. Outcomes included expected costs and survival.

RESULTS: Assuming a confirmed sepsis prevalence of 16.9% (adjudicated to Sepsis-3), the ISI strategy had an expected cost per patient of $3,849 and expected survival rate of 95.08%, whereas the procalcitonin strategy had an expected cost of $4,656 per patient and an expected survival of 94.98%. ISI was both less costly and more effective than procalcitonin, primarily because of fewer false-negative results. These results were robust in sensitivity analyses.

CONCLUSIONS: ISI was both less costly and more effective in preventing mortality than procalcitonin, primarily because of fewer false-negative results. The ISI may provide health systems with a higher-value diagnostic test in ED sepsis evaluation. Additional work is needed to validate these results in clinical practice.

KEY WORDS: decision analysis; emergency department; healthcare costs; sepsis

Sepsis remains a common and costly condition, both in terms of economic burden (1) and lives lost (2) in the United States and globally (3). Despite multiple barriers, rapid recognition is an integral component in the successful treatment of sepsis, as successful intervention is time-dependent (4). Most cases of sepsis first present in the emergency department (ED), where rapid diagnosis remains challenging, often resulting in delayed diagnosis (5). Strategies to prompt early antibiotic therapy despite diagnostic uncertainty also lead to overuse of antibiotics and straining of progressively limited hospital resources (6).

Increasingly, circulating biomarker measurements have been integrated into clinical care to improve the diagnosis and treatment of sepsis, with mixed results. In particular, procalcitonin has been proposed as a clinical test to assist early

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KEY POINTS

Question: What are the costs and consequences of using the IntelliSep Index (ISI), a novel sepsis diagnosis, compared to procalcitonin for early sepsis diagnosis in the ED?

Findings: Using a decision tree model, and assuming a sepsis prevalence of 16.9%, the ISI strategy was found to have an expected cost per patient of $3,849 and expected survival rate of 95.08%, whereas the procalcitonin strategy had an expected cost of $4,656 per patient and an expected survival of 94.98%.

Meaning: The ISI may provide health systems with a higher-value diagnostic test in ED sepsis evaluation.

identification of sepsis, despite modest sensitivity and specificity and data suggesting results do not influence clinical decision-making (7–9). The IntelliSep Index (ISI) is a novel diagnostic test that analyzes deformability characteristics of WBCs and shows promise as an early signal for sepsis. A recent clinical trial showed promising diagnostic characteristics of the ISI (10), although the assay is not yet commercially available.

Before introducing new tests to clinical care, it is necessary to understand the ability of the test to improve clinical outcomes and the effect on resource utilization. Despite promising test characteristics, it remains unknown whether ISI might improve clinical outcomes and resource utilization compared with sepsis identification strategies based on procalcitonin. The objective of this study was to perform a cost-consequence analysis and estimate the costs and survival for ISI relative to procalcitonin for early sepsis diagnosis in the ED.

MATERIALS AND METHODS

Study Design and Population

We performed decision analysis comparing two biomarker-based sepsis diagnostic strategies, procalcitonin, and ISI, in a hypothetical ED population presenting with signs or symptoms concerning sepsis. The population was calibrated to that of the population studied in a recent clinical trial of ISI in two academic medical centers in Baton Rouge, LA (10). The target population had a mean age of 62 years, was 50.2% female, and 46.9% non-White (10). This study was a mathematical model and did not involve human subjects; it is, therefore, not human subjects research under 45 Code of Federal Regulations Part 46 and is exempt from the review by institutional review board.

Model Overview

A decision tree model was used to estimate the expected costs and survival of two alternative sepsis diagnostic approaches in the ED: ISI and procalcitonin (**Fig. 1**). The first node in the decision tree—the decision node—distinguishes between use of ISI or procalcitonin to diagnose sepsis in the hypothetical ED population with concern for sepsis. We recognize that in clinical practice, procalcitonin is predominantly used to assist in antimicrobial stewardship and to help distinguish between bacterial versus viral infection, as opposed to use it as a diagnostic test for sepsis. Still, procalcitonin is an objective biomarker for sepsis and has a reasonable evidence base from which to estimate diagnostic characteristics.

If procalcitonin is used, then the result comes back positive or negative (assuming a threshold of 0.1475 ng/mL), and patients with positive results are hospitalized and treated for sepsis. A true-positive result leads to timely sepsis care, and a false-positive result results in an unnecessary hospitalization followed by discharge after a short hospital stay. Survival is a function of true sepsis status and timeliness of hospitalization. If procalcitonin returns a negative result, the patient is assumed to be discharged from the ED with or without antibiotics, at the discretion of the treating physician. A true-negative result has no additional costs or negative outcomes for the patient. A false-negative result is assumed to result in a return to the ED and a hospital admission, but given the time lost, the patient does not receive timely sepsis care. The probabilities of true- and false-positive and negative test results are estimated based on prevalence of sepsis in the population as well as sensitivity and specificity of procalcitonin using Bayes theorem.

If the ISI is used as a sepsis diagnostic, the result is band 1, band 2, or band 3. Band 1 is assumed to be a negative result and leads to discharge from the ED with or without antibiotics. If the result is a true negative, there are no additional consequences for the patient or

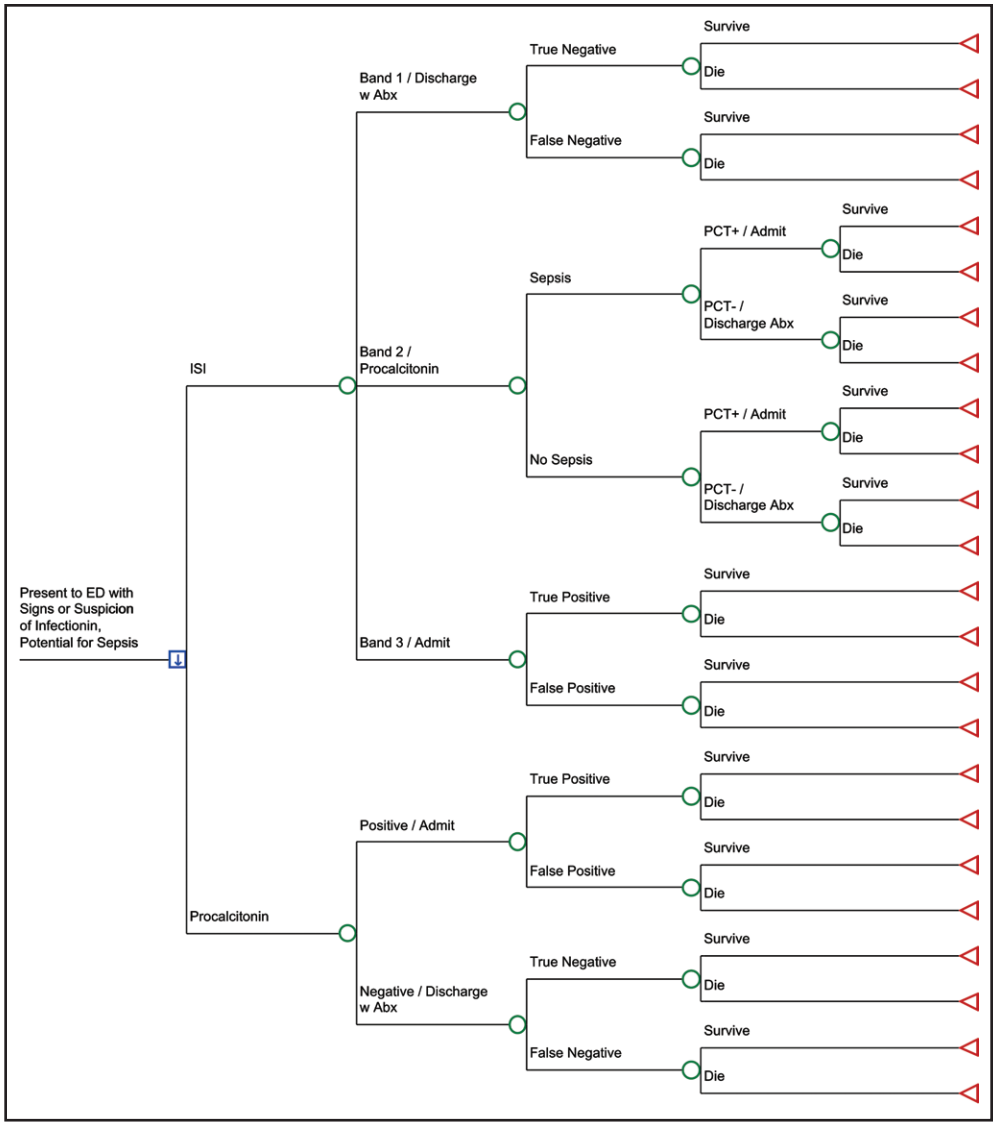

Figure 1. Decision tree model used to estimate costs and consequences of IntelliSep Index relative to procalcitonin (PCT) in diagnosis of sepsis in the emergency department (ED). Abx = antibiotics.

the provider. If the result is a false negative, the patient is assumed to return, be admitted to the hospital, and receive (delayed) sepsis care. If the ISI returns band 2, the result is deemed inconclusive and the patient is assumed to receive procalcitonin, with sequelae mirroring the procalcitonin strategy. A band 3 ISI result is assumed to be a positive test and is assumed to result in admission to the hospital. If the result is a true positive, the patient is assumed to receive timely care; if the result is a false positive, the patient is assumed to be discharged after a short stay. The probabilities of true- and false-positive and negative results from band 1, band 2, and band 3 are estimated from the prevalence of sepsis in the population reported in Guillou et al (10), as well as the sensitivity and specificity of the bands, using Bayes theorem.

Model Parameters

Model parameters are presented in **Table 1** and were derived from the best available recent literature. Although the price of ISI is not yet determined, the base case model assumed the price would be $100, and a wide range of uncertainty was explored in sensitivity analyses. Costs associated with different outcomes were estimated from an analysis of data on patients with a primary diagnosis of sepsis in the Healthcare Cost and Utilization Project National Inpatient Sample from the Agency for Healthcare Research and Quality (11). Thus, costs were estimated from the perspective of the healthcare system and were adjusted to reflect 2018 U.S. dollars. The time horizon was very short term, approximately 1 month from presentation at the ED. Patients who had false-positive results were assumed to have a 3-day hospital stay that cost $7,206.07, patients who had sepsis with a timely hospital admission had a 5-day hospitalization that cost $11,457.69, and patients with sepsis who did not receive timely care were assumed to have a 7-day hospital stay that cost $15,709.31. These assumptions were based on O'Neal et al (12), who reported that in a population presenting to the ED with signs and symptoms of sepsis, of 28 days, patients with sepsis had a mean of 22 hospital-free days, and patients without sepsis had a mean of 25 hospital-free days. We extrapolated this to 3 hospital days for patients without sepsis, 5 days for patients with sepsis who received timely care, and

TABLE 1.
Model Parameters, Values, and Distributions Used in Base Case and Sensitivity Analyses

Parameter	Base Case	Range	Distribution	Source
Prevalence of sepsis	16.9%	1–30%	Beta (43, 212)	Guillou et al (2021)
Sensitivity				
Procalcitonin	74.8%	50–100%	Beta (352, 118)	Kim et al (2018)
ISI				
Band 1	9.3%	0–50%	Beta (4, 39)	Guillou et al (2021)
Band 2	37.2%	0–50%	Beta (16, 27)	Guillou et al (2021)
Band 3	53.5%	25–75%	Beta (23, 20)	Guillou et al (2021)
Specificity				
Procalcitonin	63.8%	50–100%	Beta (396, 224)	Kim et al (2018)
ISI				
Band 1	37.3%	0–50%	Beta (79, 133)	Guillou et al (2021)
Band 2	76.4%	50–100%	Beta (162, 50)	Guillou et al (2021)
Band 3	86.3%	50–100%	Beta (183, 29)	Guillou et al (2021)
Mortality				
No sepsis	0.6%	0–5%	Beta (730, 114,270)	Usman (2018)
Sepsis with timely care	24.6%	5–45%	Beta (1,163, 3,565)	Ferrer (2014)
Sepsis with delayed care	33.1%	10–50%	Beta (741, 1,498)	Ferrer (2014)
Costs				
Procalcitonin	$25.00	$10–50	–	
ISI	$100.00	$10–1,000	–	Assumption
False-positive admission	$7,206.07	$2,500–10,000	Gamma (25, 0.0049)	NIS Analysis
Timely sepsis admission	$11,457.69	$5,000–20,000	Gamma (24.999, 0.0018)	NIS Analysis
Late sepsis admission	$15,709.31	$10,000–30,000	Gamma (25, 0.0008)	NIS Analysis
Death	$7,358.01	$5,000–15,000	Gamma (25, 0.0034)	NIS Analysis

ISI = IntelliSep Index, NIS = National Inpatient Sample.

7 days for patients with sepsis who received delayed care. Patients who died incurred additional costs of $7,358.01 regardless of timeliness of care.

Analysis

The decision model was used to estimate the expected costs and expected rate of survival for each diagnostic strategy. To understand how sensitive the results were to the baseline parameters, several deterministic sensitivity analyses were performed. Each model parameter was varied over a reasonable range (Table 1) to determine whether there was a threshold value where the optimal decision shifted from one diagnostic strategy to the other. Two-way sensitivity analyses were also performed to explore the optimal decision over combinations of sensitivity and specificity of procalcitonin. A structural sensitivity analysis was also conducted in which band 2 results were treated as if they represent negative and positive results, respectively. Finally, we performed a probabilistic sensitivity analysis (PSA). The PSA assumed models were probability distributions, which were parameterized using data from Guillou et al The analysis took 10,000 draws from these distributions and computed the probability that each strategy was optimal. All analyses were performed using TreeAge Pro software (TreeAge LLC, Williamstown, MA).

RESULTS

The expected cost for the ISI strategy was $3,849 per patient compared with $4,656 per patient for the

procalcitonin strategy. In addition, the expected rate of survival was 95.08% for the ISI strategy and 94.98% for the procalcitonin strategy. Thus, the ISI strategy was dominant (less costly and more effective) than the procalcitonin strategy in the base case.

A series of sensitivity analyses evaluated model results under changing sepsis prevalence and cost conditions. As the prevalence of sepsis ranged from 0 to 50%, the ISI strategy remained less costly than the procalcitonin strategy (**Fig. 2**). ISI also yielded a higher survival rate over the same range of prevalence (Fig. 2). The ISI strategy remained the lower-cost approach over a range of procalcitonin prices from $0 to 100 (**Fig. 3**). Likewise, the ISI strategy was less costly over the entire range of timely hospitalization, late hospitalization, and in-hospital mortality costs (**Fig. 4**). In particular, higher values for the cost of false-positive sepsis diagnostic test results led to much higher costs for procalcitonin than for ISI. This is largely driven by the higher sensitivity of ISI band 1 and band 3 results. Also, as long as the price of ISI remained below $900, ISI was the lower-cost strategy; procalcitonin became the low-cost strategy if the price of ISI rose above $900.

Supplemental Figure 1 (http://links.lww.com/CCX/B216) presents a set of one-way sensitivity analyses for in-hospital mortality. ISI remained the lower-cost strategy over the entire range of in-hospital mortality with timely care (panel A). However, as in-hospital mortality with timely care increased, the procalcitonin strategy eventually achieved a higher expected survival (panel B). In-hospital mortality must be higher for timely care than for late care to cross this threshold. A similar pattern was seen for in-hospital mortality with late care (panel C); the ISI strategy remained the lower-cost strategy over the entire range of in-hospital mortality for late care examined (panel C). However, if in-hospital mortality with late care fell below the rate of in-hospital mortality with timely care, then the procalcitonin strategy achieved a higher expected survival in the ISI strategy (panel D).

Figure 5 presents two-way sensitivity analyses of sensitivity and specificity of procalcitonin. As long as the specificity of procalcitonin was below 84%, the ISI was the lower-cost strategy. In addition, as long as the sensitivity of procalcitonin remained below 84% then the ISI strategy achieved a higher survival rate and was the optimal strategy.

A sensitivity analysis was conducted assuming that band 2 results were treated as negative and positive results, respectively. Treating band 2 results as negative yielded a higher survival rate for ISI (95.30%) and lower expected costs per patient ($3,213.78); treating band 2 results as positive also resulted in a higher expected survival rate (95.67%) but at higher expected costs per patient ($4,551.60).

A PSA was performed by assuming model parameters were distributed as described in Table 1. Results

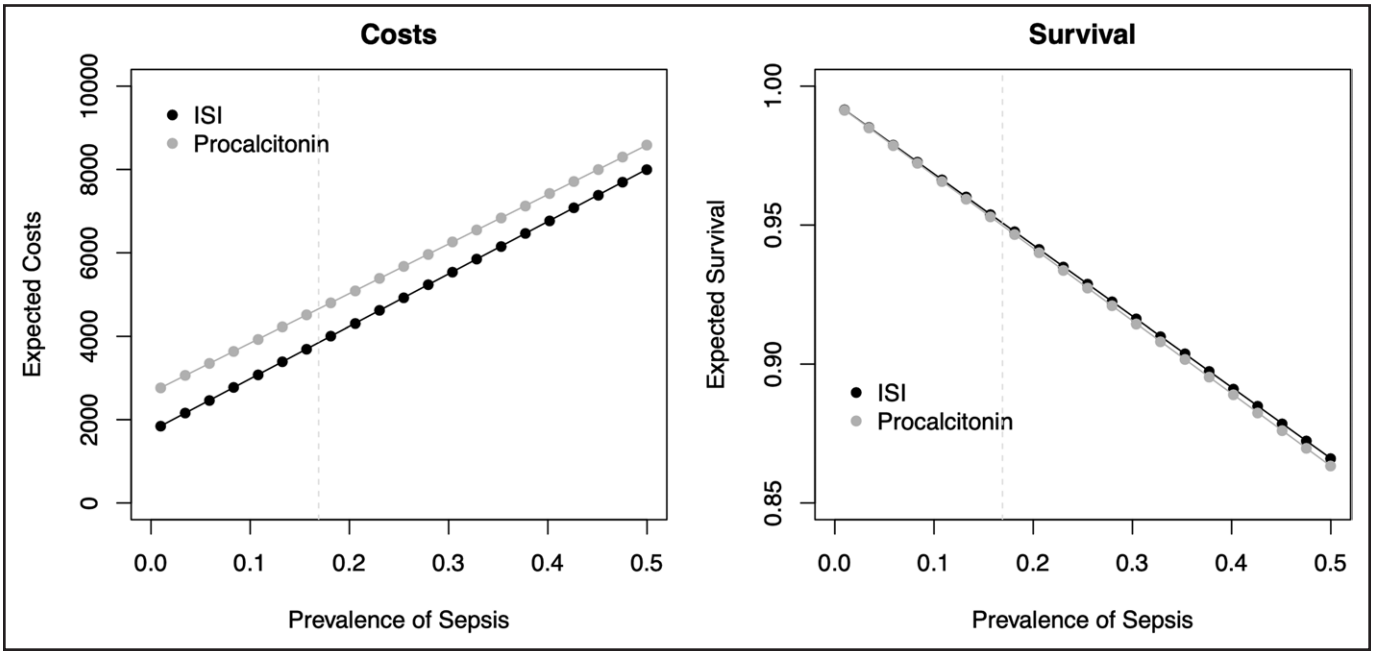

Figure 2. One-way sensitivity analyses of prevalence of sepsis in the population. ISI = IntelliSep Index.

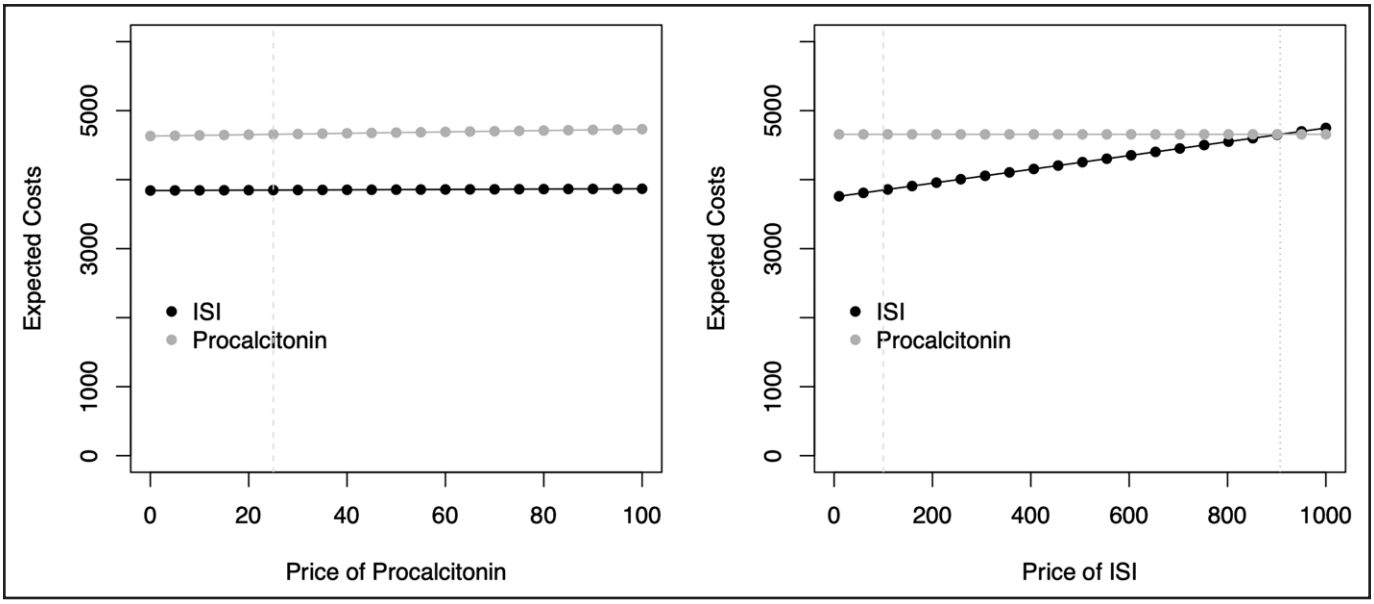

Figure 3. One-way sensitivity analysis of the price of diagnostic tests for sepsis. ISI = IntelliSep Index.

in Supplemental Figure 1 (http://links.lww.com/CCX/B216) suggest that after accounting for global parameter uncertainty, the ISI approach was 15.4 times (93.9% vs 6.1%) more likely to be less costly, and 31.5% more likely (56.8% vs 43.2%) to have lower mortality.

DISCUSSION

This study supports the hypothesis that an ISI diagnostic strategy may provide effective reductions in the clinical and financial burden of treating sepsis when compared with a procalcitonin diagnostic strategy. When compared with using procalcitonin in our model, the ISI resulted in both decreased cost and increased survival, with both outcomes improved over a wide range of cost input assumptions and performance characteristics for each laboratory test.

The majority of sepsis admissions originate from the ED (13), and improving rapid recognition and risk stratification of potentially septic patients in this setting could improve both outcomes and costs (14). The ISI has been validated as a diagnostic marker of sepsis for patients presenting to the ED with possible sepsis. The result is standardized into three interpretation bands (band 1, band 2, and band 3 corresponding to low, intermediate, and high probability of sepsis) with reproducible results. In contrast, procalcitonin has been postulated as a biomarker for guiding the treatment of acute respiratory infection, and previous efforts have evaluated the utility of procalcitonin for the risk stratification of patients with possible sepsis in the ED. However, the widespread implementation of these protocols has been difficult because of variability in procalcitonin threshold values used for diagnosis and risk stratification (15). In addition, some of these protocols require serial procalcitonin measurements, limiting their utility in the ED (8, 9, 16, 17). Finally, procalcitonin levels, even when very high, may not correlate well with severity of illness, raising concern for procalcitonin's utility in guiding such treatment decisions as prioritization or level of care for admission (18). These attributes are in contrast to the ISI, which, in addition to being a validated and standardized sepsis diagnostic, also correlates well with severity of illness as measured by standardized severity of illness scoring systems (Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation-II) and clinical outcomes, including hospital admission, ICU admission, and hospital length of stay (10, 12).

With its high mortality and disproportionate impact on the healthcare workforce, the burden of sepsis is more than financial. Systematic improvements in sepsis care are essential components to reduce unnecessary clinical variability, limit the financial burden of sepsis on patients and healthcare systems, and create a reproducible and efficient care delivery model. Protocolized care for septic patients has already been shown to both improve outcomes and reduce overall

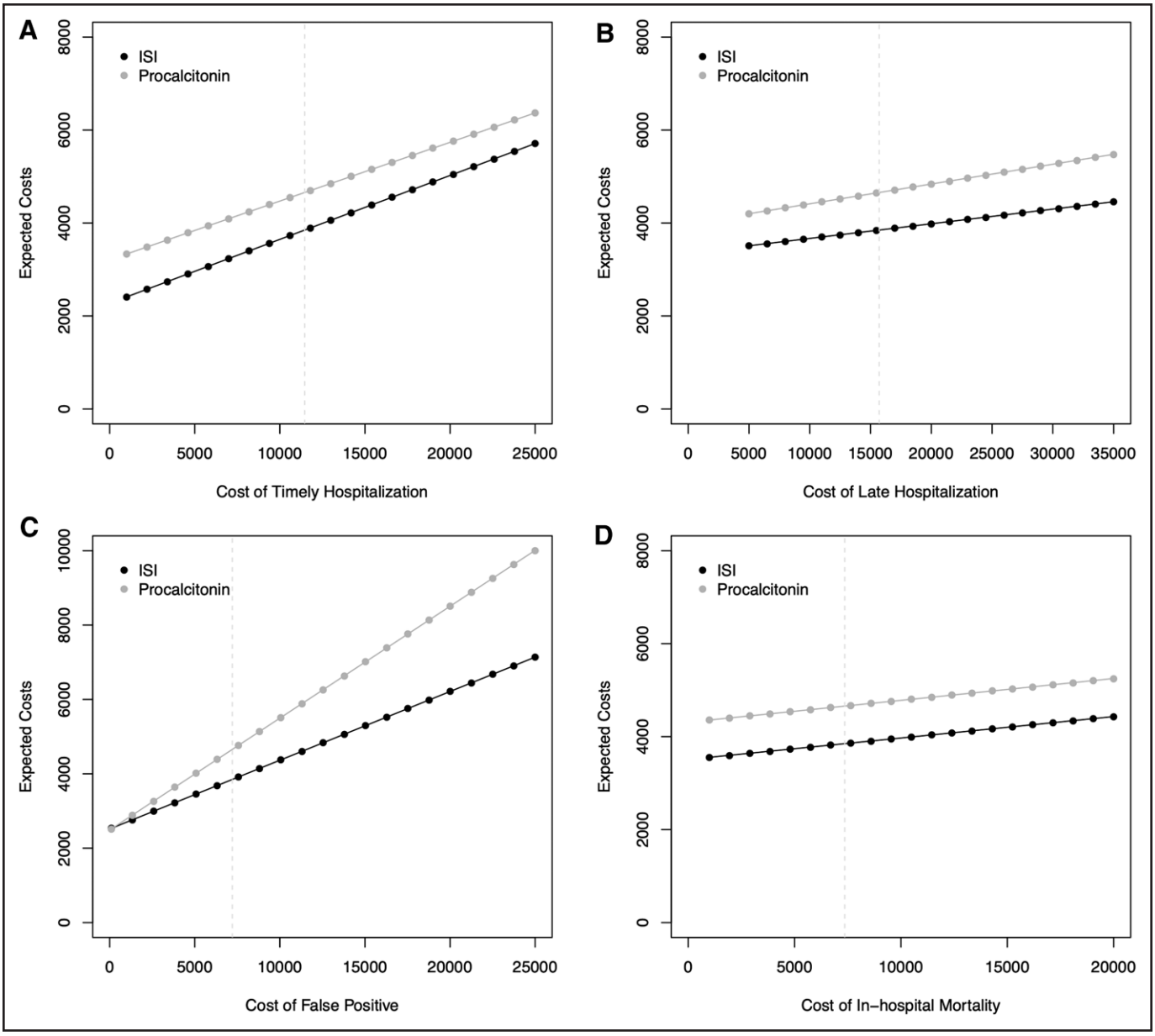

Figure 4. One-way sensitivity analyses of the costs of hospitalization. ISI = IntelliSep Index.

costs (19), and consensus guidelines exist for guiding sepsis care (20); however, there is concern that the indiscriminate application of these protocols and guidelines may result in the overuse of constrained resources and broad-spectrum antibiotics and IV fluids, further straining overtaxed EDs (21). An objective mechanism for the identification of high-risk patients is necessary for the optimal application of these limited resources without adversely impacting outcomes. This study suggests risk stratification with an ISI-based strategy could improve survival for patients with sepsis as compared with procalcitonin for all reasonable estimates of survival with relation to timeliness of care. This finding is important given that outcomes in sepsis have been proven to be dependent upon prompt recognition and action (22). Thus, delayed appropriate care should result in worse survival outcomes than timely appropriate care. In our model, for procalcitonin to be associated with superior survival, delayed care would need to be superior to timely care.

Our study has many strengths. The parameters of the model were based on data derived from a diverse group of patients enrolled through a high-volume ED into a prospective cohort for the validation of the ISI as a diagnostic for sepsis (10). Since no reference standard for the diagnosis of sepsis exists, all patients

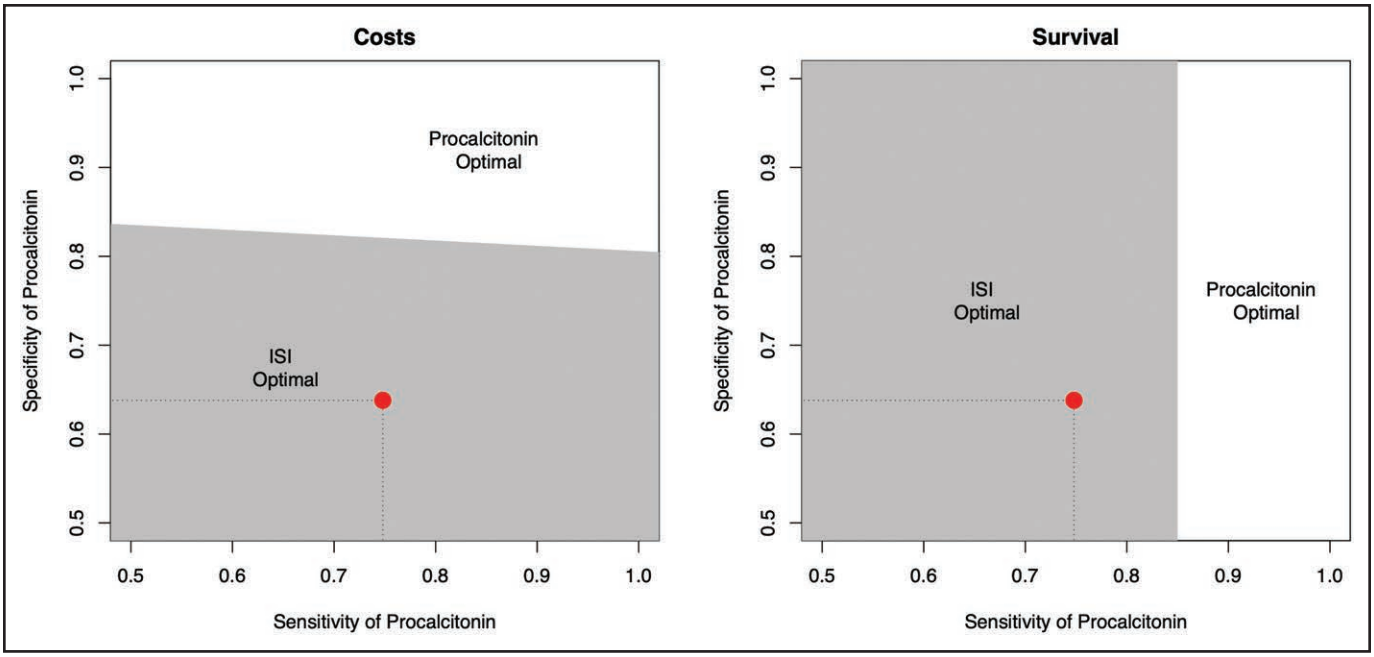

Figure 5. Two-way sensitivity analysis of the sensitivity and specificity of procalcitonin. Base case values are indicated in *red*. ISI = IntelliSep Index.

underwent a rigorous adjudication process for the determination of the disease state (septic or not septic) that involved retrospective review of laboratory tests, cultures, and imaging results by two independent physicians (10). Procalcitonin levels were obtained at the time of enrollment on the majority of patients as part of the research protocol, not only as standard of care. Finally, estimates of mortality and cost were derived from published sources. Despite these strengths, there are also weaknesses. Our model cannot account for all clinical factors that influence cost, length of stay, and mortality, and must simplify the decision-making process and certain clinical parameters, including length of stay and cost of care, both of which are difficult to assess on a large scale (23). In some settings, pathology will guide decision-making in addition to blood tests; for the sake of parsimony, this has not been accounted for in the model. Also, the model requires several assumptions, for instance, that sepsis is the only consideration in the differential diagnosis, whereas in reality, many conditions may present similar to sepsis and result in admission. Although we have tried to use the best available data for these model parameters, the results can only be as strong as the best available evidence. Furthermore, we assume that the discharge of septic patients from the ED is associated with poor outcome. Because the decision to admit or discharge a patient is complex and dependent upon a number of factors (not only the diagnosis of sepsis), some patients who meet criteria for sepsis may be safely discharged to home, though we assume that doing so is more likely associated with adverse outcomes (24). There are also limitations in the set of comparators. As mentioned earlier, procalcitonin is more likely to be used to assist in antimicrobial stewardship and to help distinguish between bacterial versus viral infection, as opposed to use as a diagnostic test for sepsis. EDs are more likely to rely on clinical expertise and suspicion for sepsis diagnosis. There are no published studies that we are aware of that report reliable data on diagnostic characteristics of clinical gestalt. If such data become available in the future it could be added as a comparator strategy. Finally, our study assumes that the only outcomes are survival and death, and does not account for such outcomes as discharge to nursing home or intermediate care facilities.

CONCLUSIONS

The search for solutions and improvements in sepsis care has become increasingly complicated, as the incidence of sepsis continues to rise due to increased awareness, changes in the risk profile of the population such as increasing age and comorbidities, and the impact of the COVID-19 pandemic on pre-existing workforce shortages (25–29). Solutions that will safely

reduce the cost of care without sacrificing outcomes will require addressing the many factors driving the soaring economic burden of the disease in this new, postpandemic era of medicine. Additionally, these solutions should facilitate treatment of the condition according to consensus guidelines (20). The ISI could serve as an invaluable element of sepsis care by quickly and efficiently focusing care on those with the highest risk of the condition while expediting the care of those with lower risk.

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