

## Development of a Model-Based Clinical Sepsis Biomarker for Critically Ill Patients

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### Abstract

Sepsis occurs frequently in the intensive care unit (ICU) and is a leading cause of admission, mortality, and cost. Treatment guidelines recommend early intervention, however positive blood culture results may take up to 48 hours. Insulin sensitivity ( $S_I$ ) is known to decrease with worsening condition and could thus be used to aid diagnosis. Some glycemic control protocols are able to accurately identify insulin sensitivity in real-time.

Hourly model-based insulin sensitivity  $S_I$  values were calculated from glycemic control data of 36 patients with sepsis. The hourly  $S_I$  is compared to the hourly sepsis score (ss) for these patients (ss = 0-4 for increasing severity). A multivariate clinical biomarker was also developed to maximize the discrimination between different ss groups. Receiver operator characteristic (ROC) curves for severe sepsis (ss  $\geq$  2) are created for both  $S_I$  and the multivariate clinical biomarker.

Insulin sensitivity as a sepsis biomarker for diagnosis of severe sepsis achieves a 50% sensitivity, 76% specificity, 4.8% positive predictive value (PPV), and 98.3% negative predictive value (NPV) at an  $S_I$  cut-off value of 0.00013 L/mU/min. Multivariate clinical biomarker combining  $S_I$ , temperature, heart rate, respiratory rate, blood pressure, and their respective hourly rates of change achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV. Thus, the multivariate clinical biomarker provides an effective real-time negative predictive diagnostic for severe sepsis. Examination of both inter- and intra-patient statistical distribution of this biomarker and sepsis score shows potential avenues to improve the positive predictive value.

### Keywords:

sepsis, insulin sensitivity, biomarker, diagnosis, receiver operator characteristic, glucose control, real-time clinical application.

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## 1. INTRODUCTION

Sepsis presents a serious medical problem in the adult intensive care unit (ICU) around the world, with a 11-15% incidence of severe sepsis, 30-60% mortality rate, \$22,100 USD average cost per case, \$16.7 billion USD annual total cost, and 1.5% projected annual incidence increase [1]. Sepsis treatment guidelines and patient management protocols recommend early goal-directed resuscitation of the septic patient during the first 6 hours after infection recognition [2]. Currently, blood bacteria cultures are considered the gold standard for confirmation of infection. However, only 51% of sepsis cases are positively identified as cultured pathogens [3].

Early interventions have been documented to reduce mortality from 46.5% to 30.5% [4]. In addition, a landmark clinical trial implementing a blood glucose control protocol resulted in a reduction in the incidence of sepsis [5]. Currently available biomarkers, such as procalcitonin (PCT), provide sepsis diagnostic test results in 2-3 hours with commercially available kits, but to various levels of clinical accuracy [6].

A clinically validated glucose-insulin model that is able to model insulin sensitivity ( $S_I$ ) in real-time has been used to develop blood glucose protocols for critically ill patients [7, 8]. An integral-based parameter identification method has been used to fit the data [9]. The model-based  $S_I$  has been observed to indicate the severity of illness and metabolic status, as well as being validated against euglycaemic clamp data [10]. Insulin sensitivity has also been previously documented as decreasing with worsening condition [11], and increasing with improvement [12, 13].

This study aims to evaluate the relationship of modelled insulin sensitivity [7, 14] and patient condition. In particular, this study examines using the modelled insulin sensitivity as a marker for real-time diagnosis and differentiation of Systemic Inflammatory Response Syndrome (SIRS) and sepsis in a cohort of adult ICU patients. It extends the work of Blakemore et al. [15] by increasing discrimination and utilizing additional clinical measurements.

## 2. METHODS

### 2.1 Physiological glucose-insulin model

The physiological glucose-insulin model for clinically ill patients has one compartment for plasma glucose, two compartments for insulin kinetics, and a two-compartment dextrose absorption model.

$$\dot{G} = -p_G G - S_I G \frac{Q}{1 + \alpha_G Q} + \frac{P(t) + EGP_b - CNS}{V_G} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V_I} + e^{-k_I u_{ex}(t)} I_B \quad (3)$$

$$\dot{P1} = -d_1 P1 + D(t) \quad (4)$$

$$\dot{P}2 = -\min(d_2 P2, P_{\max}) + d_1 P(1) \quad (5)$$

$$P(t) = \min(d_2 P2, P_{\max}) \quad (6)$$

Equation (1) represents the plasma glucose compartment where  $G$  is the blood glucose level. Equation (2) describes the plasma insulin compartment where  $I$  is the plasma insulin level. Equation (3) describes insulin action in interstitial space where  $Q$  is the interstitial insulin level. Equations (4)-(6) describe the absorption of dextrose intake ( $D(t)$ ) through stomach (compartment  $P1$ ) and gut (compartment  $P2$ ) and its appearance into plasma ( $P(t)$ ). The transport of glucose from gut to the blood stream is saturable, and the maximum transport rate is  $P_{\max}$ .

Endogenous glucose production ( $EGP$ ) for a healthy subject varies throughout a day according to daily activities, food intake and stress response etc. On a pharmacodynamics level,  $EGP$  is suppressed with increasing  $G$  and  $Q$ . Time-varying  $EGP$  is difficult to measure clinically and cannot be uniquely identified in this study. Therefore this model uses a constant term  $EGP_b$  in Equation (1) to represent the basal endogenous glucose production for a patient under no presence of glucose or insulin. Insulin independent glucose removal (excluding central nervous system uptake  $CNS$ ) and the suppression of  $EGP$  from  $EGP_b$  with respect to  $G$  are represented with  $p_G$ . In contrast, insulin mediated glucose removal and the suppression of  $EGP$  from  $EGP_b$  due to GLUT4 (which action is associated with the compounding effect of receptor-binding insulin and blood glucose) is represented with  $S_I$ . Insulin sensitivity ( $S_I$ ) is time varying and reflects evolving patient condition.

In Equation (3), the exogenous insulin administration into plasma insulin is  $u_{ex}(t)$ . Plasma insulin decay rate is  $n$  and  $V_I$  is the plasma insulin distribution volume. Endogenous insulin production is expressed by  $e^{-k_I u_{ex}(t)} I_B$ , where  $I_B$  is the basal insulin production when no exogenous insulin is present. Endogenous insulin production is suppressed exponentially with exogenous insulin. Table 1 is a nomenclature for all the parameters, symbols and abbreviation used in this article.

This model is an improvement from the model used in [15]. This model has an additional  $CNS$  for glucose uptake as this uptake is found to be very consistent inter- and intra-individuals. Dextrose absorption model describes by Equations (4)-(6) is more physiological and universal compare to the simple feed model in [15]. The simple feed model in [15] requires the enteral feeding be relatively constant (not changing more frequently than every 2 hours), whereas the dextrose absorption model presented here is generic and applicable even for modelling meal intake. Finally, this model has an endogenous insulin term  $e^{-k_I u_{ex}(t)} I_B$  to ensure the entire differential equations model in Equations (1)-(6) is not ill-conditioned when there is no exogenous insulin given over a significant period of time.

**Table 1. Nomenclature**

$\alpha_G$	Saturation parameter for insulin mediated glucose removal	(L/mU)
$\alpha_I$	Saturation parameter for insulin clearance from plasma	(L/mU)
CDF	Cumulative distribution function	
CNS	Central nervous system glucose uptake	(mmol/min)
$D(t)$	Dextrose intake	(mmol/min)
$d_1$	Glucose absorption rate from stomach	(min <sup>-1</sup> )
$d_2$	Glucose absorption rate from gut	(min <sup>-1</sup> )
$EGP$	Endogenous glucose production	
$EGP_b$	Basal endogenous glucose production rate	(mmol/min)
FN	False negative	
FP	False positive	
$G$	Blood glucose level	(mmol/L)
GLUT	Glucose transporters	
ICU	Intensive Care Unit	
$I$	Plasma insulin level	(mU/L)
$I_B$	Basal endogenous insulin production rate	(mU/min/L)
$k$	Interstitial insulin transport rate	(min <sup>-1</sup> )
$k_I$	Exponential suppression of endogenous insulin production constant	
$n$	Plasma insulin decay rate	(min <sup>-1</sup> )
NPV	Negative predictive value	
$P(t)$	Glucose appearance in plasma from dextrose intake	(mmol/min)
$P_1$	Glucose level in stomach	(mmol)
$P_2$	Glucose level in gut	(mmol)
PCT	procalcitonin	
PDF	Probability density function	
$p_G$	Insulin independent glucose removal (excluding central nervous system uptake) and the suppression of $EGP$ from $EGP_b$ with respect to $G$	(min <sup>-1</sup> )
$P_{max}$	Maximal glucose flux from gut to plasma	(mmol/min)
PPV	Positive predictive value	
$Q$	Interstitial insulin level	(mU/L)
ROC	Receiver operator characteristic	
$S_I$	Insulin mediated glucose removal and the suppression of $EGP$ from $EGP_b$ with respect to $G$ and $Q$	(L/mU/min)
SIRS	Systemic inflammatory response score	
SOFA	Sepsis-related organ failure assessment	
$ss$	Sepsis score	
TN	True negative	
TP	True positive	
$u_{ex}(t)$	Exogenous insulin	(mU/min)
$V_I$	Plasma insulin distribution volume	(L)
$V_G$	Plasma glucose distribution volume	(L)

## 2.2 Sepsis score ( $ss$ ) criteria and analysis

Sepsis is a systemic inflammatory response syndrome (SIRS) due to infection [16]. In this study, sepsis is defined using the clinical classification score ( $ss$ ) provided by the ACCP/SCCM guideline definitions [17]. The criteria are defined in Tables 2-4, which include SIRS and the Sepsis-related Organ Failure Assessment (SOFA) score [18].

**Table 2. SIRS criteria**

score	Criteria	
+ 1	temperature	< 36° C > 38° C
+ 1	heart rate	> 90/min
+ 1	respiratory rate or PaCO <sub>2</sub>	> 20/min < 32 mm Hg
+ 1	white blood cell count	< 4 x 10 <sup>9</sup> /L or > 12 x 10 <sup>9</sup> /L or presence of > 10% immature granulocytes

**Table 3. SOFA criteria**

score	system	criteria	
+ 1	cardiovascular	MAP <sup>a</sup> or need for inotropes	< 60 mm Hg
+ 1	respiratory	PaO <sub>2</sub> /FiO <sub>2</sub>	<250 mm Hg/mm Hg <200 mm Hg/mm Hg with pneumonia
+ 1	renal	Urine output	< 0.5 ml/kg/h
+ 1	blood	platelets	< 80 x 10 <sup>9</sup> /L or 50% drop in 3 days
<sup>a</sup> Mean arterial pressure			

**Table 4. Sepsis score (ss) criteria**

sepsis score	SIRS > 2	Infection during stay	organ failure > 1	fluid resuscitation	inotrope present	high inotrope dose <sup>a</sup>
0	normal					
1	sepsis	X	X			
2	severe sepsis	X	X	X	X	
3	septic shock	X	X	X	X	
4	refractory septic shock	X	X	X	X	X
<sup>a</sup> adrenaline or noradrenaline > 0.2 mg min <sup>-1</sup> kg <sup>-1</sup>						

Clinical data was gathered for n = 36 sepsis patients admitted to the medical ICU in Christchurch Hospital (Christchurch, New Zealand). Each patient was on the SPRINT blood glucose control protocol [13], providing 9208 total patient hours of hourly modelled insulin sensitivity. The hourly S<sub>I</sub> was compared to SIRS and ss data. Note that each stay included periods of sepsis and without sepsis (ss = 0). These periods are differentiated by positive blood culture and SIRS ≥ 2, and thus ss ≥ 1.

Receiver Operator Characteristic (ROC) curves were used to examine the performance of S<sub>I</sub> as a diagnostic marker for sepsis. ROC curves effectively examine the ability of the biomarker to differentiate between populations. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also evaluated. ROC curves effectively examine the separation between normal and diseased populations in terms of probability density functions (PDF). Variability of ss score from one hour to the next hour were also examined.

Therefore, other clinical measurements were evaluated and combined with  $S_I$  to create a biomarker that aims to maximise the PDF separation or discrimination in normal and septic groups. The biomarker was created as an hourly changing function based on hourly  $S_I$  and clinical measurements. A linear recursive least square method was used to maximize the discrimination between populations. Optimal weighing functions were chosen using the Optimization Toolbox in Matlab<sup>TM</sup>. The specific goal was to provide discrimination for  $ss \geq 2$ , where prior studies [15] only achieved it for  $ss \geq 3$ . Achieving this goal for the lower  $ss = 2$  value will provide a marker for a larger group of patients.

Ideally, cross validation or bootstrapping should be performed on the data to avoid overfitting. However, because the current available data is very limited (36 patients), the same data is used for both developing the biomarker and testing it. In particular, the low prevalence of high sepsis score hours limits the ability to boot strap or cross validate effectively. Equally, it should be noted the work presented in this study is more of a proof-of-concept study to justify a larger, more costly comprehensive validation study, rather than a comprehensive large scale validation. The method used in this work is novel in the field of sepsis diagnosis, to the best of the authors' knowledge. Finally, sepsis patient data used in this study is a subset from a cohort representative of typical intensive care patients [13].

### 3. RESULTS AND DISCUSSION

Table 5 shows the total hours at each sepsis score. The majority of the hours are at  $ss < 2$ .

**Table 5. Patient hours by sepsis score (ss)**

sepsis score (ss)	0	1	2	3	4
patient hours	4186 (45.1%)	4861 (52.3%)	91 (1.0%)	88 (0.9%)	60 (0.6%)

#### 3.1 Insulin sensitivity ( $S_I$ ) and sepsis score (ss)

Figure 1 shows a cumulative distribution function (CDF) plot of  $S_I$ , for each ss group.  $S_I$  is generally lower for more severe sepsis. However, the distinction between the septic ( $ss \geq 1$ ) and non-septic ( $ss = 0$ ) groups is not clear.

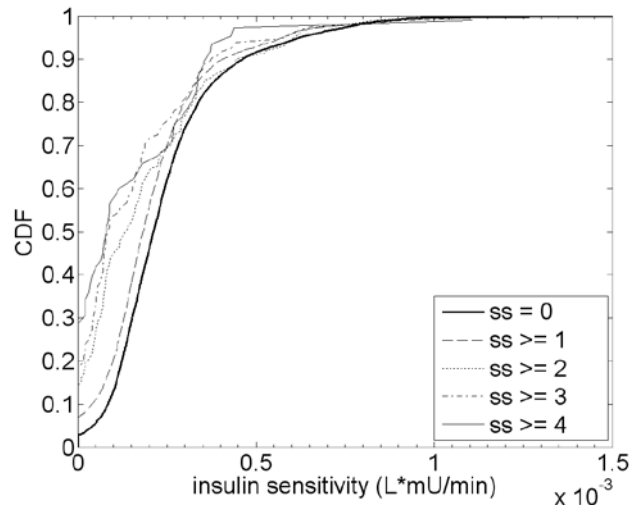


Fig. 1. Cumulative distribution function (CDF) of insulin sensitivity ( $S_I$ ), grouped by sepsis score (ss).

### 3.2 Insulin sensitivity $S_I$ as a biomarker

Figure 2 shows the ROC curve for  $S_I$  as a sepsis biomarker. There is minimal discrimination between no sepsis ( $ss = 0$ ) and a sepsis score of  $ss = 1$ . For  $ss \geq 2$ , an  $S_I$  cut-off value of 0.00013 L/mU/min achieves a 50% sensitivity, 76% specificity, 4.8% PPV, and 98.3% NPV.

Even though  $S_I$  is generally lower at higher  $ss$  values, the distribution of  $S_I$  for each  $ss$  group overlaps too much in Figure 1 with the non septic group. Therefore, using  $S_I$  level itself is not a completely effective sepsis biomarker.

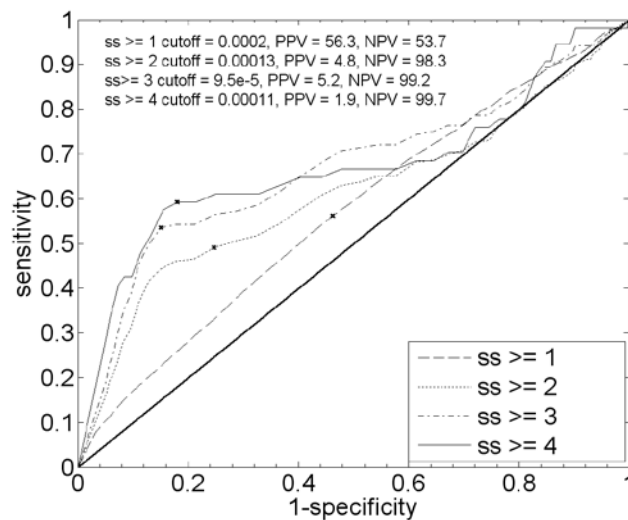


Fig. 2. Receiver operator characteristic (ROC) curve for  $S_I$  as a sepsis biomarker, grouped by sepsis score (ss), with cutoff points (x).

### 3.3 Multivariate clinical biomarker utilising $S_I$

Figure 3 shows the CDF of a biomarker combining  $S_I$  and other clinical factors, for each  $ss$  group. The clinical measurements used in the biomarker include temperature, heart rate, respiratory rate, blood pressure, and their respective rates of change. The multivariate biomarker generally decreases with increasing sepsis severity. The discrimination between sepsis and non-septic groups is improved, as compared to Figure 1 using  $S_I$  only as a diagnostic test.

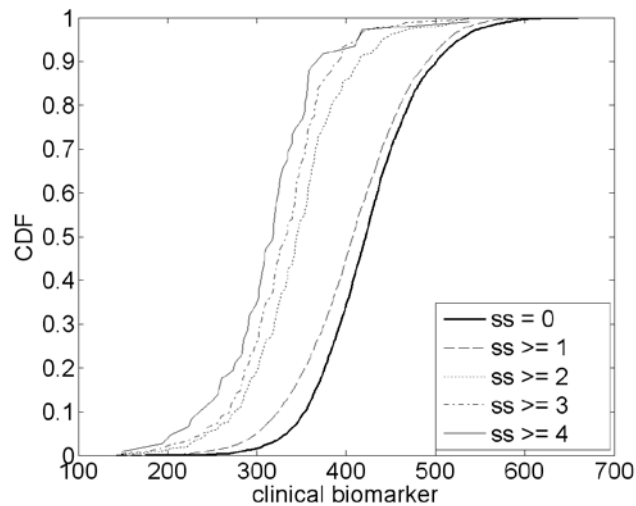


Fig. 3. Cumulative distribution function (CDF) of the clinical biomarker, grouped by sepsis score ( $ss$ ).

Figure 4 shows the ROC curve for this biomarker. For  $ss \geq 2$ , the biomarker achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV. The addition of clinical measurements with  $S_I$  significantly improved the diagnostic test performance for sepsis, as compared to using  $S_I$  alone. In particular, the biomarker provides an effective negative predictive diagnosis for severe sepsis ( $ss = 2$ ), which was not achieved previously.

It is also clear comparing Figure 2 and Figure 4 that the discrimination between  $ss = 1$  and  $ss \geq 2$  is now wider. Note that  $ss = 1$  is difficult to discriminate from  $ss = 0$  and simple, clinical SIRS. Hence, as seen in Figure 2 and Figure 4, its discrimination from  $ss = 0$  is still marginal.



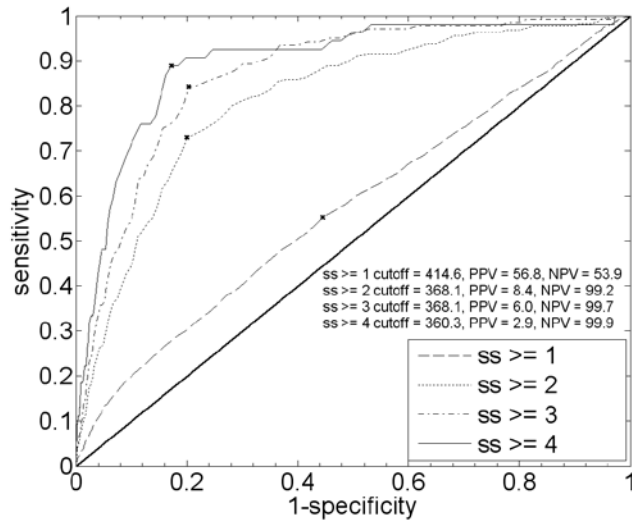


Fig. 4. Receiver operator characteristic (ROC) curve for the multivariate clinical biomarker, grouped by sepsis score (ss), with cutoff points (x).

Table 6 is a contingency table showing the biomarker diagnostic outcome for  $ss \geq 2$ . There are 9208 total hours of patient data. This data is classified into four categories using sepsis score and biomarker test outcome: true positive (TP,  $n = 165$ ), false positive (FP,  $n = 1802$ ), false negative (FN,  $n = 61$ ), and true negative (TN,  $n = 7180$ ). There are 8982 hours when  $ss < 2$  and 226 hours when  $ss \geq 2$ . Using the biomarker, 7241 hours test negative and 1967 hours test positive.

**Table 6. Contingency table**

	$ss \geq 2$ 226 hours	$ss < 2$ 8982 hours	
test positive 1967 hours	TP = 165 (1.8%)	FP = 1802 (19.6%)	PPV 8.4%
test negative 7241 hours	FN = 61 (0.7%)	TN = 7180 (78%)	NPV 99.2%
total 9208 hours	sensitivity 73.0%	specificity 79.9%	

Note that these ratios also indicate the relative incidence and reflect clinical expectations where, by the hour, most sepsis is not necessarily severe. This last point is critical as most sepsis incidence is recorded by patients. By patient, the incidence of severe sepsis is 5-10% [1], which is reflected in this cohort. However, with rapid, aggressive treatment its incidence by hour is low. This low incidence is problematic in developing such a non-invasive and real-time clinical biomarker.

Figure 5 provides a visual presentation of clinical sepsis score and the biomarker performance. Most of the patient hours are  $ss < 2$  (TN + FP). Even though the biomarker correctly identifies the severity of sepsis 73% of the time when  $ss \geq 2$  and 80% of the time when  $ss < 2$ , the PPV stays low because the ratio of TP to test positive is limited by the ratio between  $ss \geq 2$  to  $ss < 2$ . On contrast, NPV is inherently high because the ratio of TN makes up the majority of test negative. Again, the mathematics indicate that

relatively low incidence by hour, as seen in the 8982 hours of  $ss < 2$  and 4186 hours of  $ss = 0$ , hinders good PPV despite good specificity.

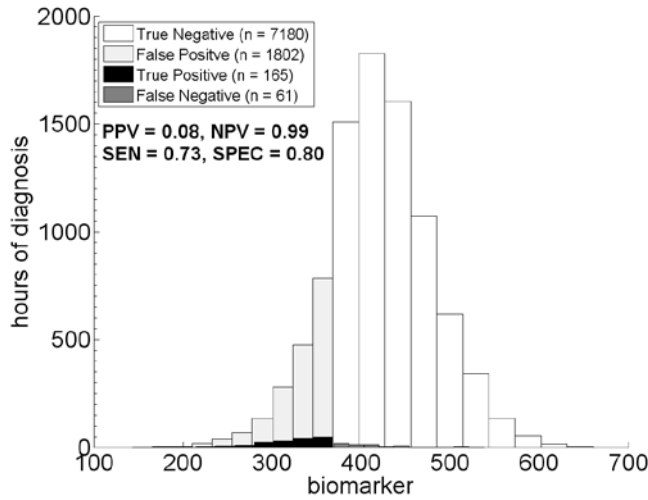


Fig. 5. Histogram of clinical biomarker data, grouped by contingency results.

### 3.4 Sepsis time course

Figure 6 effectively shows the probability of how  $ss$  changes from one hour to the next. The horizontal axis is the current hour  $ss$  and the vertical axis is the  $ss$  for the next hour. The majority of the patient data is when  $ss = 0$  and  $ss = 1$ .

Patients at  $ss = 1$  tend to stay at  $ss = 1$ , and patients having  $ss = 0$  tend to stay at  $ss = 0$ . Interestingly, when  $ss \geq 2$ , the highest probability is moving to  $ss = 1$  in the next hour. This set of results shows that if sepsis is detected at  $ss \geq 2$ , current rapid and aggressive ICU treatments are usually very effective in reducing the severity of the inflammatory responses.

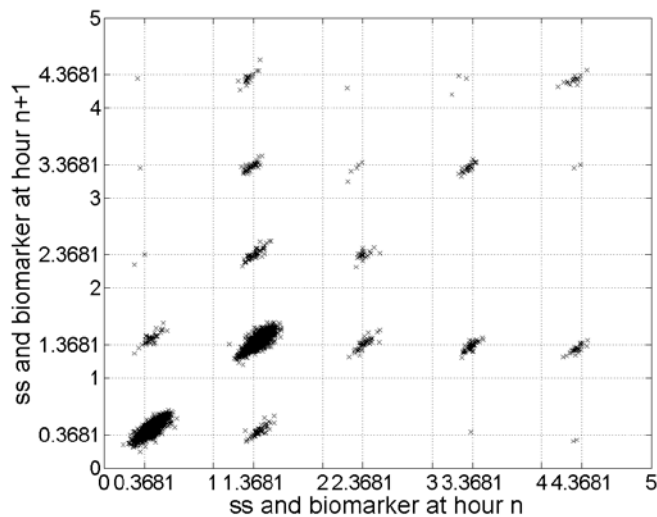


Fig. 6. Scatter plot of clinical biomarker variation from hour to hour with respect to sepsis score (ss) (axis numbers = ss + biomarker/1000).

### 3.5 Biomarker comparison

The clinical informative values a biomarker may provide in sepsis are: detection of infection; diagnosis of SIRS severity and infection progression; and patient treatment guidance, responsiveness, and prognosis. One such investigated biomarker is procalcitonin (PCT), which was first found elevated in sepsis in 1993 [19]. PCT is a precursor of the hormone calcitonin, synthesized by thyroid C cells, but in sepsis has an extra-tyroidal origin. Upon intravenous injection of endotoxin from *E. coli* in healthy volunteers, serum PCT becomes detectable after 4 hours, maintaining a plateau through 8 to 24 hours, following an increase of proinflammatory cytokines [20].

PCT can be measured from serum plasma by commercially available immunoluminometric assay kits such as LUMitest PCT (Brahms, Berlin, Germany) and Kryptor PCT (Brahms, Hennigsdorf, Germany). The use of PCT has been approved by the FDA “in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock”.

The reported diagnostic power of PCT from 25 studies using PCT (2,966 patients) as a diagnostic marker of sepsis, severe sepsis, or septic shock in the adult ICU or after surgery or multiple trauma, compared with nonseptic SIRS has sensitivity ranging from 42% to 97% or even 100%, and specificity ranging from 48% to 100% [21]. Optimal cutoff values for PCT, determined from ROC curves, ranged from 0.6 to 5 ng/mL.

PCT is generally only assessed once a day and thus cannot provide real-time detection. In contrast, the biomarker presented in this study is a real-time marker. In addition, all of these studies had some form of extensive clinical pre-screening for sepsis and/or SIRS, biasing the sensitivity or specificity. The overall results reported are no better, and often worse, than those reported here.

Traditionally, diagnostic test results are based on a cut-off point. This method effectively treats all patients as a single, generic person with one clear cut-off point that distinguishes between normal and abnormal states. However, recent medical treatments have been moving towards patient customisation – tailoring treatments to patient needs [22]. Although this study has so far provided a sepsis biomarker that has a cut-off value which can differentiate  $ss \geq 2$  from  $ss < 2$  most of the time, this biomarker is also a time-varying value. As with most clinical measurements, this biomarker would have both inter- and intra-patient statistical distribution.

### 3.6 Future work

It is therefore of interest to further investigate how this biomarker changes through time for patients, and how much variability there is between patients. A means of normalizing patients and likely changes using stochastic models would improve biomarker performance. An observational study and follow-up of a biomarker for sepsis diagnosis in the ICU would provide the data needed for that analysis. Finally, the statistical model of a

biomarker, like the one developed in this paper, may be more useful clinically by providing a probability analysis of disease progression in real-time.

#### 4. CONCLUSIONS

Insulin sensitivity as a sepsis biomarker for diagnosis of severe sepsis achieves a 50% sensitivity, 76% specificity, 4.8% PPV, and 98.3% NPV at an  $S_I$  cut-off value of 0.00013 L/mU/min. A discriminating threshold was not found between the  $ss = 0$  and  $ss = 1$  cohorts due to a high degree of population overlap. A clinical biomarker combining  $S_I$ , temperature, heart rate, respiratory rate, blood pressure, and the respective rate of change achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV, and thus can act as an effective negative predictive diagnosis for severe sepsis.

PPV performance is poor because the ratio of true positive to test positive is limited by the ratio of hours where  $ss \geq 2$  to  $ss < 2$ . The majority of patient hours had  $ss < 2$ . However, the multivariate clinical biomarker may provide patient-specific diagnosis, and effectively show the probability of sepsis time course from hour to hour. Real-time results may aid in the treatment and management of sepsis in the ICU. Future work includes an observational study and follow-up of a biomarker for sepsis diagnosis in the ICU.

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