Model-based Insulin Sensitivity as a Sepsis Diagnostic in Critical Care

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Abbreviations:

- APACHE II - Acute Physiology and Chronic Health Evaluation II
- CRP – C Reactive Protein
- EGP – Endogenous Glucose Production
- ICU – Intensive Care Unit
- IL-6 – Interleuken-6
- IL-8 – Interleuken-8
- MAP – Mean Arterial Pressure
- PCT – Procalcitonin
- ROC – Receiver Operating Characteristic
- S_I – Insulin Sensitivity (model-based metric)
- SS_I – Simple Insulin Sensitivity (hand calculated metric)
- *ss* – Sepsis Score
- SIRS – Systemic Inflammatory Response Syndrome
- SPRINT – Specialised Relative Insulin + Nutrition Tables
- TNFα – Tumor Necrosis Factor α
- PDA – Personal Digital Assistant

ABSTRACT

BACKGROUND

Timely diagnosis and treatment of sepsis in critical care requires significant clinical effort, experience and resources. Insulin sensitivity is known to decrease with worsening condition and could thus be used to aid diagnosis. Some glycaemic control protocols are able to identify insulin sensitivity in real time.

METHODS

ROC curves and cutoff insulin sensitivity values for diagnosing sepsis were calculated for model based insulin sensitivity (S_I) and a simpler metric (SS_I) that was estimated from the glycaemic control data of 30 patients with sepsis and can be calculated in real time without use of a computer. Results were compared to the insulin sensitivity profiles of a general ICU population of 113 patients without sepsis and the 30 patients with sepsis, comprising a total of 26,453 patient hours. The patients with sepsis are identified as having sepsis based on a sepsis score (*ss*) of 3 or higher (*ss* = 0-4 for increasing severity). Patients with Type I or Type II diabetes were excluded. Ethics approval for this study was granted by the South Island Regional Ethics Committee

RESULTS

ROC cutoff values of $S_I = 8\text{x}10^{-5}$ L mU^{-1} min^{-1} and $SS_I = 2.8\text{x}10^{-4}$ L mU^{-1} min^{-1} were determined for $ss \geq 3$. Model-based S_I fell below this value in 15% of all patient hours. The S_I test has a negative predictive value of 99.8% The test sensitivity is 78% and specificity is 82%. However, the positive predictor value was 2.8%. Slightly lower sensitivity (68.8%) and specificity (81.7%), but equally good negative prediction (99.7%), were obtained for the estimated SS_I.

CONCLUSIONS

Insulin sensitivity provides a negative predictive diagnostic for sepsis. High insulin sensitivity rules out sepsis for the majority of patient hours and may be determined non-invasively in real-time from glycaemic control protocol data. Low insulin sensitivity is not an effective diagnostic, as it can equally mark the presence of sepsis or other conditions.

INTRODUCTION

Severe sepsis and septic shock has a high incidence rate and high mortality rate in an ICU [1-3]. The cost of treating sepsis and of additional bed hours required in sepsis patients is reported to be $16.7 billion dollars in the United States [1]. Insulin control protocols have been widely used to tightly control blood glucose values [4-10], which has shown to result in a reduction in the incidence of sepsis [10].

Diagnosis of sepsis presents many challenges in a clinical setting. A positive culture should precede the use of antibiotics [3], but blood culture results take 24-48 hours, or longer, to process [2]. More rapid diagnosis can be achieved using a variety of biomarkers, such as TNFα, IL-6, IL-8, CRP and PCT, with varying success, but a minimum lag time of typically 2-3 hours is still present [2]. Therefore, other signs must be investigated to assist in making the most timely diagnosis and potentially starting appropriate treatments, such as fluid resuscitation, and vasopressor and inotrope use. The earlier these interventions are correctly applied, the better the mortality outcome [11, 12]. Rivers et al [12] found that early goal-directed treatment of sepsis reduced mortality from 46.5% to 30.5%.

The negative effect of sepsis on insulin sensitivity and glucose metabolism is well documented [13-15]. However, the mechanisms by which this takes place are not fully understood. It has been suggested that sepsis induces a counterregulatory hormone response causing the reduction in insulin sensitivity [13, 16]. There is also a delay reported between the introduction of

endotoxins and the onset of increased insulin resistance [13, 17]. Low insulin sensitivity can also be exacerbated by the use of glucocorticoids [18, 19], which are sometimes indicated in the treatment of severe sepsis [3]. Finally, the inflammatory nature of the acute immune response to sepsis can also have a hyperglycaemic effect [17, 20]. Thus insulin sensitivity and sepsis are strongly linked, but its effectiveness as a diagnostic is unknown.

Insulin sensitivity can be found using lumped parameter compartment models that have had extensive clinical validation in critical care [5, 8, 21-24]. In such models, varying insulin sensitivity is the driving dynamic. Alternatively, glycaemic control protocols usually provide some measure of insulin sensitivity in real time. An example of one such protocol is SPRINT, which regulates enteral nutrition rates and insulin boluses [4, 5, 23]. Enteral nutrition and insulin are modulated according to the patient's current blood glucose level and the change in blood glucose level as well as prior hour interventions, and an insulin sensitivity metric may also be derived from these input data. This insulin sensitivity information, whether model based or estimated from intervention data, is available without additional invasive procedures, outside of those required for glucose control.

METHOD

Identifying insulin sensitivity requires capturing the fundamental dynamics of the glucose regulatory system. The model given in Equations 1-5 is algebraically equivalent to the model employed and validated by Chase et al. [21, 22, 25] and Lonergan et al. [5, 23].

$$\dot{G}_t = -p_G G_t - S_I G_t \frac{Q}{1+\alpha_G Q} + \frac{P(t)}{V_G} + P_{end} \quad (1)$$

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

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}}{V} \quad (3)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \overline{P}_{i+1} < \overline{P}_i \quad (4)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pr}(t-t_i)} \text{ where } \overline{P}_{i+1} > \overline{P}_i \quad (5)$$

Where $G_t(t)$ [mmol/L] is the plasma glucose and $I(t)$ [mmol/L] is the plasma insulin resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. The effect of previously infused insulin being utilised over time is represented by $Q(t)$ [mU/L], with k [1/min] accounting for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I [L/(mU.min)], respectively. P_{end} is endogenous glucose production (EGP), which is held at a constant 3 mg min^{-1} kg^{-1} from a measured population constant obtained from the results of Chambrier et al [14] for a glucose distribution volume of V_G = 13.65 L.. The parameter V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)] which is obtained from enteral nutritional input rates which are adjusted hourly to 1 of 8 discretised enteral nutrition rates. From recorded hourly volume rates and known caloric densities, plasma glucose inputs can be calculated from Equations 4 and 5. Michaelis-Menten functions are used to model saturation, with α_I [L/mU] used for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose

clearance [26, 27].

Patient specific profiles for time-varying S_I can be generated from retrospective data using this model to create virtual patients to test trial protocols [22, 25, 28]. For identified S_I profiles in this study, p_G, k, n, P_{end}, I, V and V_G are set to generic population values [21, 25, 26, 28]. Upper and lower physiological limits of 1e-3 and 1e-5 L mU^{-1} min^{-1} are imposed on identified S_I values [28]. A 3 hourly moving average smoothing is applied to the resulting S_I profiles to mitigate the effects of glucose measurement noise.

S_I profiles are calculated for a cohort of 143 patients in the Christchurch Hospital ICU who had been on the SPRINT protocol. All patients with previously diagnosed diabetes were excluded from the study to remove any bias from their lower insulin sensitivity due to diabetes. The mean APACHE II score was 20.4 and the range was 4-43. The average length of stay was 10.9 days with a range of 0.3-59 days. Ethics approval was granted by the South Island Regional Ethics Committee for this retrospective data analysis.

In this cohort, a subset of 30 patients who potentially had sepsis during their hospital stay was identified using positive blood culture results and/or in the absence of these, the judgment of experienced senior intensive care clinicians. Comprehensive clinical data for these patients was examined to isolate the time and duration of sepsis**.**

From this clinical data, a sepsis classification score (*ss*) was generated for each

hour of the patients stay that strictly follows the American College of Chest Physicians/Society of Critical Care Medicine guideline definitions of 1992 and 2003 [29, 30]. The criteria for the sepsis score (*ss*) are defined in Tables 1-3. The organ failure criteria scoring in Table 2 uses the most relevant elements of the definitions for the Sepsis-related Organ Failure Assessment (SOFA) score [31]. The sepsis score thus includes Systemic Inflammatory Response Score (SIRS) and SOFA organ failure criteria, as well as including factors for treatments indicated in sepsis. Thus, it provides better correlation than any single criterion [30].

In Table 1, a tick indicates a necessary criterion and all necessary criteria must be present to attain the indicated score. For example, a patient only on fluid resuscitation would attain a sepsis score of 0. For this study, the diagnosis of sepsis is a sepsis score of 3 or more. This *ss*=3 value corresponds to a SIRS score of 2 or more, an organ failure score of 1 or greater, fluid resuscitation and inotrope use of any amount all at the time of investigation, and an infection during the patient's ICU stay. Tables 2 and 3 define the organ failure and SIRS scores utilized in this overall score.

For this 30 patient sepsis cohort, the mean APACHE II score was 22 with a range of 7-40. The mean length of stay was 11.7 days with a range of 0.7-59 days. The mean sepsis score for this subset was 0.5 throughout their stay. However, 45 patient hours had a sepsis score of 3 or higher at some point in their stay. From this information, a Receiver Operating Characteristic (ROC) curve was drawn for the 30 patients using the model-based insulin sensitivity,

(S_I) as the marker, and a sepsis score of $ss \geq 3$ as the diagnostic. A ROC curve plots the sensitivity of a diagnostic test against 1-specificity, which is equivalent to the true positive rate plotted against the false positive rate, for all possible cutoff values. A completely random test is represented as a line at 45 degrees to each axis, representing an additional false positive result for each false negative result eliminated. A perfect test (100% specificity and 100% sensitivity) is a vertical line up the sensitivity axis at 1-specificity=0 and then a horizontal line along the 1-specificity axis, allowing selection of a cutoff with a zero false positive rate and a zero false negative rate.

This ROC curve was compared to a similar one obtained for the estimated insulin sensitivity identified by the SPRINT protocol (SS_I) given by Equation 7. This approximated insulin sensitivity is evaluated only at times that the change in glucose is less than the measurement error of 7% (ie. $\dot{G} = 0$) [32]. Equation 7 then results from algebraic rearrangement of Equation 1 using the assumption that endogenous clearance and production is negligible and ignoring saturation effects in steady state. When blood glucose is not available at any hour, the last reading taken is used. The number of patient hours which satisfy the $\dot{G} = 0$ criteria are shown in Table 4.

$$SS_I = P(t)\frac{60}{I(t)G_t} \tag{7}$$

Hence, Equation 7 represents an approximated S_I value in steady state.

RESULTS

Figure 1 and Table 5 shows the insulin sensitivity distributions for 130 patients compared with APACHE II score, discretising the patient set into 9 groups of APACHE II scores. Note that the remaining 13 patients are not included in the APACHE II score groups due to unavailable APACHE II score data. None of these 13 were in the 30 patient sepsis cohort. Figure 1 shows the high density of low S_I readings found in all groups with APACHE II greater than 6.

The ROC curve for model-based S_I data from 6744 patient hours is shown in Figure 2. The sensitivity of the insulin sensitivity test was found to be 77.8% and the specificity, 82.2%. The positive predictive value was 2.8% and the negative predictive value was 99.8%. The cutoff value for this test was an S_I of 8e-5 L mU^{-1} min^{-1}. Over 85% of the 26,453 identified insulin sensitivity values for the general ICU cohort (143 patients, with and without sepsis) were above the 8e-5 L mU^{-1} min^{-1} cutoff.

The SS_I ROC curve for the applicable 2036 patient hours that $\frac{G_i - G_{i-1}}{G_i} < 7\%$ is shown in Figure 3. The sensitivity of the insulin sensitivity test was found to be 68.8% and the specificity, 81.7%. The positive predictive value was 2.9% and the negative predictive value was 99.7%. The cutoff value for this test was an SS_I of 2.8e-4 L mU^{-1} min^{-1}, which is approximately 3 times higher than that for S_I in Figure 2. For 82.7% of the time, a critically ill patient's simple insulin sensitivity (SS_I) will be above this cutoff point of 2.8e-

4 L mU^{-1} min^{-1} as found from the 7529 hours of the 143 general ICU patient cohort (28% of 26,453 available hours). This 82.7% result is similar to the result for S_I over the full time period.

DISCUSSION

Absence of sepsis shows a strong correlation with a higher S_I. The ROC shown in Figure 2 indicates that insulin sensitivity can exclude a sepsis diagnosis far more accurately than it can make one. Specifically, 87% of the time in this ICU cohort it is 99.8% certain that a patient does not have sepsis ($ss \leq 2$) due to a modeled insulin sensitivity of greater than 8e-5 L mU^{-1} min^{-1}.

However, as a positive predictor, insulin sensitivity is not useful. Figure 1 shows that with increasing APACHE II scores, the lognormal distribution of S_I tends to lower S_I values (Kruskal-Wallis Test $p<0.05$). This result indicates that not only sepsis, but other severe illness and effects could be responsible for a low S_I value in a critically ill patient, causing a high number of false positives as seen by the high density of low S_I values in Figure 1. This result explains the low positive predictive value of either insulin sensitivity metric (S_I or SS_I). However, the high negative predictive value offers the clinical opportunity to avoid pre-emptive prescription of antibiotics or other treatment for sepsis, and as such is still a reasonably strong diagnostic discriminator.

The SS_I was a slightly inferior predictor to the model based S_I profiles, but the negative predictive value was still very high offering the possibility of ruling

out sepsis in 82.7% of patient hours. However, with additional data the cut-off point identified by the ROC may move significantly, but these predictive values should only change slightly. A limiting factor in this analysis is that only 16 patient hours with sepsis, out of 2036 patient hours, were available for this part of the study. This limited quantity of data is due to the requirements of non-zero enteral nutrition and insulin input and negligible changes in blood glucose for Equation 7. Overall, only approximately 30% of patient hours (30.2% of patient hours in the sepsis cohort and 32% in the complete cohort) were available to compute SS_I, creating a potential further limitation for the simpler metric.

While the sensitivity of the test remained relatively unchanged for SS_I versus S_I, the specificity dropped greatly due to a large increase in the number of false positives. This result can be partly explained by the protocol's reduced resolution. However, it is possible that another effect is due to the pool of data being reduced by the requirement that change in measured glucose is less than 7% of previous measurement (measurement error). Constant blood glucose is more likely to be found in more stable patients who are generally less likely to have sepsis. This unintended filtering in using the simplified SS_I metric increases the proportion of patients with low baseline insulin sensitivity, to patients with sepsis induced low insulin sensitivity. In particular, 40% of hours with sepsis in the sepsis cohort were eliminated by the $\dot{G} \approx 0$ criterion. This filtering also causes the discretised appearance of the ROC curve, by reducing the number of available data points, particularly periods of sepsis.

However, the insulin requirement of $I(t) \geq 0$ U/hr in Equation 7 for the estimated metric (SS_I) is not as restrictive in an ICU, as in a less acute ward setting. A 1 U/hr or greater insulin dosage is frequently called for in glycaemic control protocols and is often sustained for prolonged periods of a patients' hyperglycaemic stay. Similarly, patients will typically not spend significant periods of time fasting in an ICU. For this study, only enteral nutrition was considered; oral and parenteral nutrition were not used.

The advantage of SS_I as a predictor is that it can be very easily evaluated in real time with only a pocket calculator. Hence, a clinician can obtain useful information about a patient's condition without invasive, computationally intensive or time consuming tests. While the simple method introduces additional uncertainty by reduced resolution, as well as offering limited availability, the reduction in computational effort could justify its use over a model based approach if the computational resources were not available (eg. a PDA with program). However, a growing trend toward computation driven protocols could lead towards the regular use of the higher resolution, model-based S_I value [8, 33-35].

More specifically, the cutoff value for this test was an SS_I of 2.8e-4 L mU^{-1} min^{-1}. To use this value clinically, a simple example of two patients could be considered. The first on 80% (65 ml/hour) of goal nutrition rate and 3 U/hour of insulin under SPRINT, the second, much more insulin resistant, receives 40% (30 ml/hour) of goal feed and 5 U/hour of insulin. In the data used, the enteral nutrition was Diabetic Resource (Novartis Inc), which has 36%

(20.6g/250ml) carbohydrate content. Utilizing these values and appropriate unit conversions, Equation 7 yields SS_I = 7e-4 and SS_I = 1.6e-4, respectively. These values are well above the cutoff, as might be expected for such a glucose tolerant individual and the second, highly resistant patient is well below it. Thus, sepsis ($ss \geq 3$) would be ruled out in the first case by the negative predictive value of the test, despite other symptoms and would not be ruled out (nor ruled in) in the second case. Finally, note that without the unit conversions, the simple insertion into Equation 7 of these values provides equivalently different values, which are equally useful as SS_I if the ROC cutoff value is converted. Thus, simple data on the patient nutritional details and rates, as well as insulin given can provide a real-time clinical output.

Figure 4 shows the correlation between model S_I and SS_I. The R^2 value for the relationship is 0.68. This stronger correlation supports the similarity between the findings of the S_I and SS_I diagnostics, despite the small amount of sepsis hours available for the latter. This comparison between insulin sensitivities is for 7529 hours of the general ICU cohort of 143 patients. The comparison includes times when blood glucose values are changing by less than 7% and when insulin received is greater than 1 U/hr. The latter constraint is applied to include only times when EGP is sufficiently suppressed. If the requirement is extended to those times at which a patient receives 1.5 U/hr of insulin, the R^2 value increases to 0.78 by eliminating the outliers as shown. Additionally, the model S_I fit limits the values to 1e-5 L mU^{-1} min^{-1} $\leq S_I \leq$ 1e-3 L mU^{-1} min^{-1}, whereas SS_I is unrestricted in value. These different limits have also reduced the correlation between S_I and SS_I.

With the discretised nature of the sepsis definition used ($ss \geq 3$), it is clear that some error must be present in the derivation of the ROC curves. This error may limit the reliability of the results. However, with limited blood culture and biomarker data available due to the retrospective nature of the study, this error was unavoidable.

More specifically, for the sepsis score (*ss*) used in the study, a positive pathology culture is necessary to obtain a sepsis score of $ss = 3$. If this requirement is removed from the score and a diagnosis is defined as $ss = 3$ the diagnostic value of the test becomes:

- Sensitivity = 64%
- Specificity = 70%
- Positive predictive value = 30%
- Negative predictive value = 91%

This definition also gives 16% of all patient time as having septic shock, which is relatively high. The change in the test statistics above is likely due to the inclusion of other severe illnesses (known to also cause low S_I values) in the group of patient hours defined as having sepsis for the purpose of this study. In short, it is impossible to be specific about the presence of very severe sepsis on an hour to hour basis to develop this metric without including the positive blood culture. This criterion thus minimises the diagnosis of septic shock and sepsis being incorrectly applied in this study when a patient is

presenting with general sepsis symptoms caused by other severe illness. Finally, note that this potential limitation on the score utilised does not limit the clinical utility of the S_I or SS_I metrics presented, as this criterion is only used to validate these metrics as presented.

Figure 1 and Table 5 also present another potentially interesting result, where no significant correlation appears between insulin sensitivity, S_I, and APACHE II score. Initially, this result might appear contradictory. However, APACHE II score is typically measured at admission or in the first 24 hours, and is thus a measure of the level of illness only at that point in time. Given that a patient's level of acute illness can evolve significantly over time, such as when developing sepsis later in a patient stay, the originally measured APACHE II score may not reflect those changes. Hence, as S_I evolves dynamically over time with patient condition, any correlation to APACHE II will be lost. Additionally, low S_I can occur for a variety of reasons, not only sepsis, not all of which will have the same level of APACHE II score, also making that correlation less significant or likely.

Finally, any model-based methods will have limitations. In this case, the parameter identification method and limited available data mean that only S_I is patient-specifically identified. All other constant parameters (P_{END}, V_G, V_I, p_G, n, k, α_G, and a_I) held at population averages. The P_{END} term representing EGP is held constant for lack of other available data, but is set to the middle of the range found by Chambrier et al [14] for sepsis patients. While this value may not be accurate for all patients, in Equation 1 it has the primary affect of

shifting the results, thus raising or lowering the resulting S_I profiles identified without changing their dynamics. Dynamic endogenous effects due to changing blood glucose levels are absorbed by the p_G term in Equation 1, which ensures that these fundamental dynamics are accounted for, minimising the uptake of other effects into the studied parameter, S_I. Similar sensitivity and clinical prediction and glycemic control validation studies [21-25, 28] have been done for the other population constant values in the model, to justify the values used, as well as keeping them constant, in this study. However, greater levels of clinical data that allowed further, real-time patient specific identification of other values could add resolution to the metrics and methods presented here.

Finally, patients who have Type I or Type II diabetes were excluded from this study. If these patients were to be included it is likely that the sensitivity and positive predictive value would be even lower than at present since these patients will present with insulin resistance (at least, in Type II diabetics). The prevalence of Type II diabetes is high and disproportionately so in some ICU settings [36, 37], and it is expected that patients with Type II diabetes will have longer hospital stays due to increased insulin resistance, further limiting some of the clinical applications of this study. However this issue would not be expected to alter the negative predictive value of the metric proposed, although additional studies on these specific cohorts must be done to extend the methods here for application in those cases.

CONCLUSIONS

High insulin sensitivity can rule out the presence of sepsis in a critically-ill non-diabetic patient for the majority of their stay. Sepsis is ruled out when modelled insulin sensitivity is above S_I = 8e-5 L mU^{-1} min^{-1}. This condition is met for 85% of all patient hours in this general ICU setting. Insulin sensitivity below 8e-5 L mU^{-1} min^{-1} can be due to either sepsis or other underlying conditions. The accuracy and flexibility of model based insulin sensitivity gives better reliability as a diagnostic for sepsis. However, insulin sensitivity can be reasonably accurately evaluated using estimated methods in real time by using glycaemic control protocol data. These estimated values provide similar negative predictive values. This preliminary study shows the potential of insulin sensitivity as a diagnostic metric for sepsis when used as a negative predictor, however it will also require a larger validation study including more complete blood culture data to fully validate it for clinical use.

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Table 1. Sepsis score (*ss*) criteria

Sepsis Score (*ss*)		**Definition**					
		SIRS ≥2	Infection during stay	Organ Failure ≥1	Fluid Resuscitation	Inotrope Present	High Inotrope Dose[a]
0	Normal						
1	Sepsis	✓	✓				
2	Severe Sepsis	✓	✓	✓	✓		
3	Septic Shock	✓	✓	✓	✓	✓	
4	Refractory Septic Shock	✓	✓	✓	✓	✓	✓

[a] Adrenaline or Noradrenaline ≥ 0.2 mg min^{-1} kg^{-1}

Table 2. Organ failure criteria utilized

Score	System	Criteria	
+1	Cardiovascular	MAP OR need for inotropes	≤ 60 mm Hg
+1	Respiratory	PaO_2 /FiO_2	≤ 250 mmHg/mmHg ≤ 200 mmHg/mmHg with pneumonia
+1	Renal	Urine Output	< 0.5 mL/kg/hr
+1	Blood	Platelets	< 80 x 10^9 / L OR 50% drop in 3 days

Table 3. SIRS Criteria

Score	Criteria	
+1	Temperature	≤ 36 °C ≥ 38 °C
+1	Heart Rate	≥ 90 /min
+1	Respiratory Rate OR $PaCO_2$	≥ 20 /min ≤ 32 mm Hg
+1	White Blood Cell Count	≤ 4 x 10^9 / L OR ≥ 12 x 10^9 / L OR presence of >10% immature granulocytes

Table 4. Summary of Patient hours in each subset of the ICU cohort

	Sepsis Patients	Non-Sepsis Patients	Total
Number of Patients	30	113	143
Total Hours	6,744	19,709	26,453
Total Hours in which $\dot{G}_t = 0$	2,036	5,493	7,529

Table 5. Time spent below S_I = 8e-5 L mU^{-1} min^{-1}, the cutoff value for the sepsis score, $ss \geq 3$

APACHE II score Range	% of time below cutoff
1 – 5	2.3
6 – 10	15.3
11 – 15	8.7
16 – 20	12.7
21 – 25	14.8
26 – 30	15.3
31 – 35	20
36 – 40	15.3
41 – 45	19.8

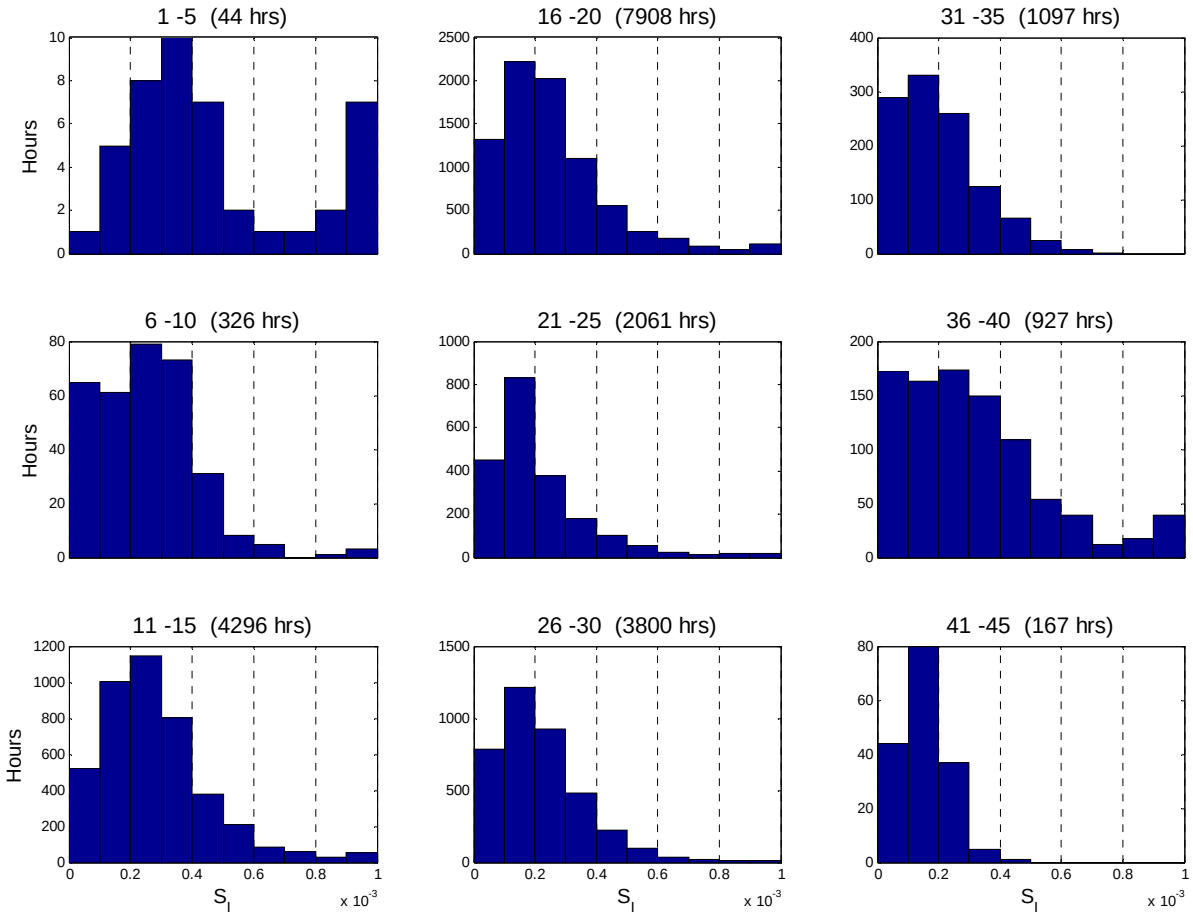

Figure 1. Insulin Sensitivity (S_I) distributions of ICU patients grouped by APACHE II scores

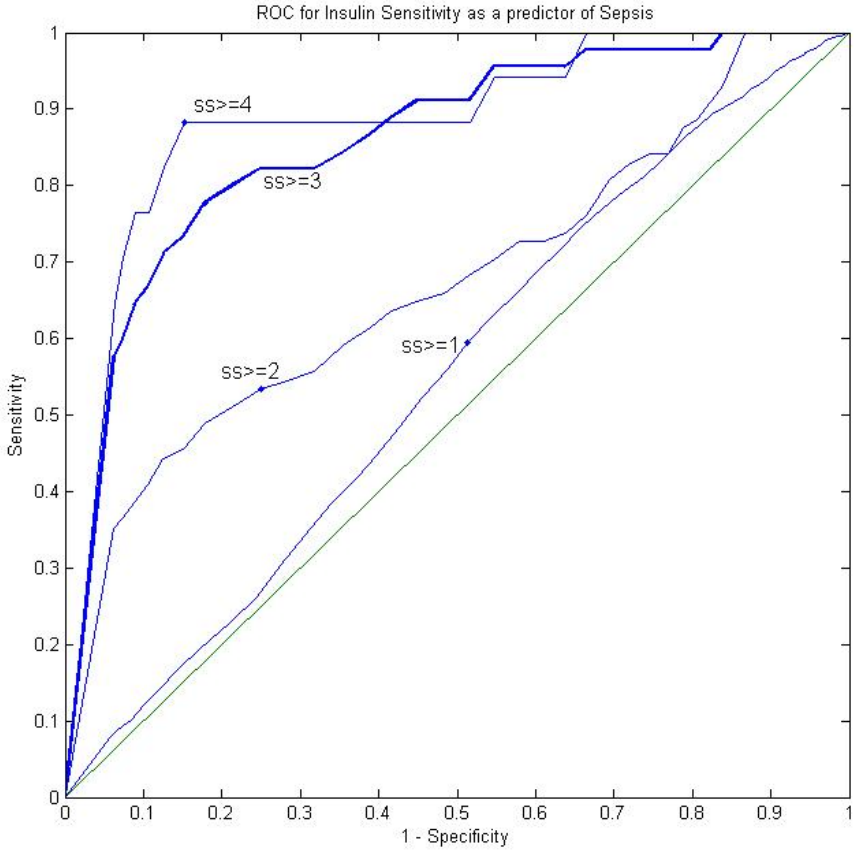

Figure 2. ROC of the modeled Insulin Sensitivity (S_I) metric as a predictor of sepsis ($ss \geq 3$)

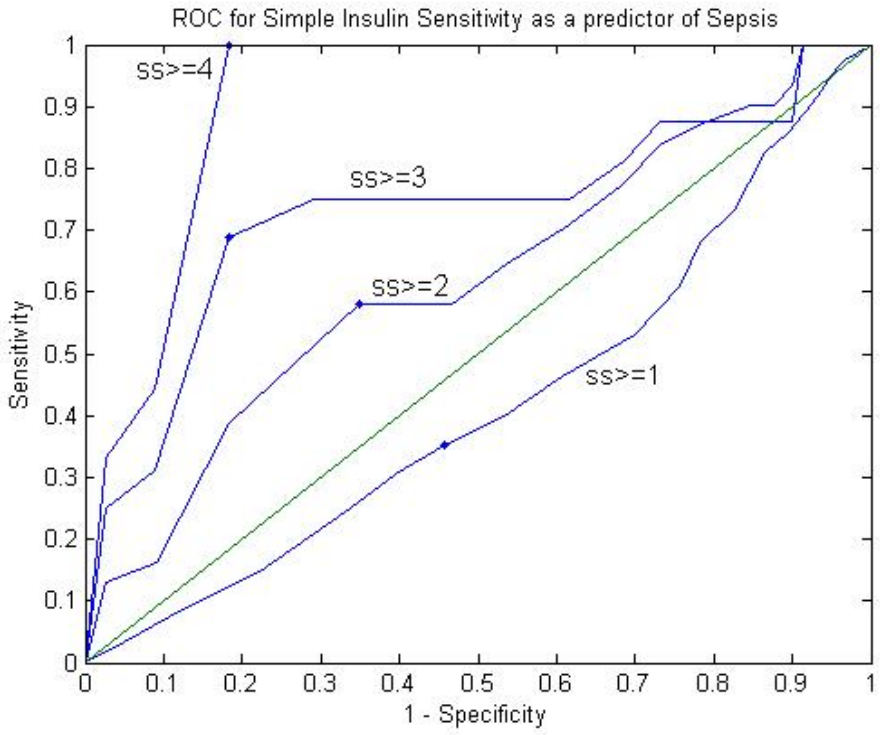

Figure 3. ROC of Insulin Sensitivity (SS_I) metric evaluated in real time as a predictor of sepsis

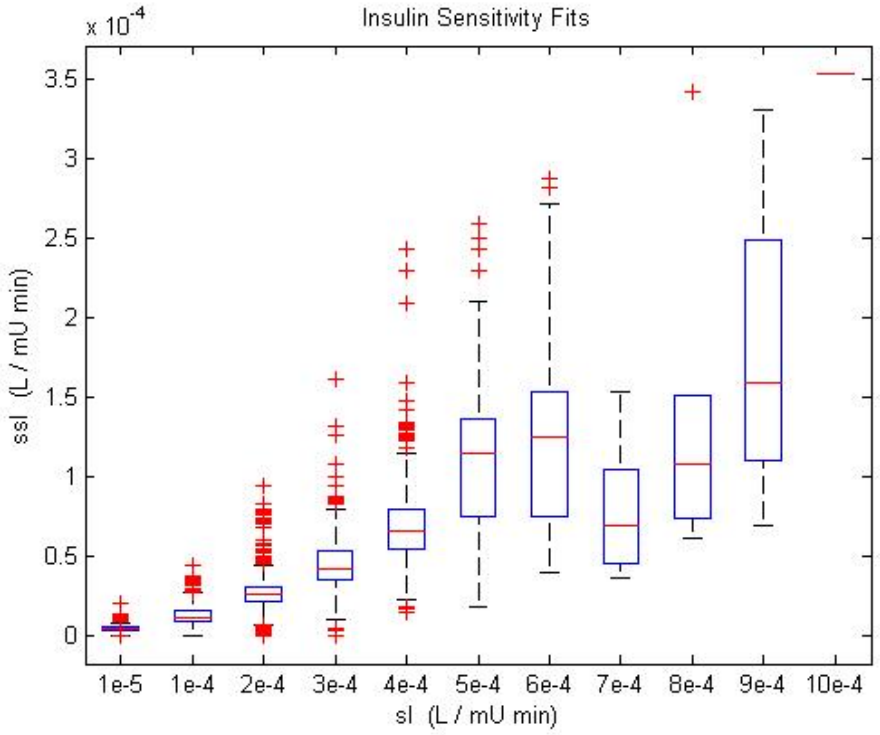

Figure 4. Correlation between SS_I and S_I the simple and model based metrics for insulin sensitivity