Insulin Sensitivity and Sepsis Score: A Correlation between Model-Based Metric and Sepsis Scoring System in Critically Ill Patients

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Abstract

Sepsis is highly correlated with mortality and morbidity. Sepsis is a clinical condition demarcated as the existence of infection and systemic inflammatory response syndrome, SIRS. Confirmation of infection requires a blood culture test, which requires incubation, and thus results take at least 48 hours for a syndrome that requires early direct treatment. Since sepsis has a strong inflammatory component, it is hypothesized that metabolic markers affected by inflammation, such as insulin sensitivity, might provide a metric for more rapid, real-time diagnosis. This study uses clinical data from 30 sepsis patients (7624 hours in ICU) of whom 60% are male. Median age and median Apache II score are 63 years and 19, respectively. Model-identified insulin sensitivity (S_I) profiles were obtained for each patient, and insulin sensitivity and its hourly changes were correlated with modified hourly sepsis scores (SS_{H1}). SI profiles and values were similar across the cohort. The sepsis score is highly variable and changes rapidly. The modified hourly sepsis score, SS_{H1}, shows a better relation with insulin sensitivity due to less fluctuation in the SIRS element. Median S_I and ΔS_I of the cohort is 4.193e-4 and 4.253e-6 L/mU.min, respectively. P-values are 0.0392 (SS_{H1} = 0, SS_{H1} = 2), 0.3337 (SS_{H1} = 0, SS_{H1} = 3), and 0.0581 (SS_{H1} = 1, SS_{H1} = 2), respectively. CDF of S_I indicates that insulin sensitivity is more significant when comparing hourly sepsis score at a very distinguish level.

Keywords

Glucose-insulin model, ICU, insulin sensitivity, sepsis, sepsis score.

Introduction

Sepsis is an increasingly common condition and a leading source of mortality and morbidity in Intensive Care Unit (ICU). The mortality rates of more than 50% have not improved in the past 30 years, despite intense research advances in treatment. Additionally, sepsis is common cause of death particularly in non-coronary ICU [1] and highly associated with mortality in critically ill patients [2-4].

Infection and systemic inflammatory responses (SIRS) are the main elements of sepsis. Infection is produced by the invasion of tissue or fluid by pathogenic microorganisms [5]. In contrast, SIRS is related with a response of the immune system to infection, which is highly related to organ dysfunction and organ failure [5,6], which also occur frequently with and without sepsis. However, in many cases, infection is suspected without being able to be microbiologically confirmed for several reasons, creating so-called "culture negative" sepsis [7] and further complicating diagnosis.

Sepsis has been classified into several stages, including sepsis, severe sepsis, septic shock, and refractory septic shock. Despite the definition of sepsis and its classification, these terms do not precisely characterize the patient's stage and condition, and may be confounded by other issues. More specifically, sepsis, at all levels, is a syndrome or collection of conditions. Grouped together as "sepsis" they categorize patients with a significantly increased risk of death. Hence, unfortunately perhaps, sepsis is as much of a patient category as it is a specific physiological condition. This issue makes sepsis diagnosis quite difficult.

According to Rivers and colleagues [8], early goal-directed treatment (EGDT) provide better outcome by reducing mortality from 46.5% to 30.5% of sepsis cases. Clinical studies on septic shock by Rivers et al. [8] observed lower mortality rates in patients assigned to EGDT (42.3%) compared to standard therapy (56.8%). Even if they survive, sepsis usually reduces quality life [9-12], especially if not specifically treated. However, some studies [13-15] unable to repeat the results of Rivers et al. [8], indicating that early treatment is highly subject to patient conditions but still necessary in sepsis.

Nevertheless, diagnosing sepsis in critical care has many challenges. The long process of obtaining blood culture results can delay care and the resulting lack of knowledge makes optimizing antibiotic or other treatments difficult. However, blood culture results are still the most accepted gold standard to clinically diagnose infection. Therefore, the inability to guarantee accurate, early diagnosis affects treatment selection, patient condition, and thus outcomes. What needed is a rapid test or a readily available parameter that can provide insight for clinicians to determine appropriate treatment and medications.

Several studies have shown that model-based S_I (insulin sensitivity) can be used as an indicator for severity of illness, as this metabolic marker is reflective of the inflammatory state in these patients. In particular, Blakemore et al. [16] have shown that insulin sensitivity of a patient decreased as the patient condition worsens. Moreover, it has been previously documented that S_I decreases with worsening condition and increases with improvement in patient condition [17-

20], even though its more common use is in model-based treatment of hyperglycemia [20]. This important information can be used to correlate between a patient condition and other complications, which are highly associated with hyperglycemia.

In this study, the relationship between model-based insulin sensitivity and a clinically accepted parameter, sepsis score is investigated. More specifically, a clinically validated model-based S_I [21-25] and its hourly evolution have been compared and examined to determine the relationship between sepsis score and another modified sepsis score that can be used for hourly intervention. If there is a clear relation between insulin sensitivity and sepsis score, S_I can therefore become a marker to evaluate sepsis progression in real-time.

Materials and Methods

i. Glucose-Insulin System Model

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

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

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

The system model used in this analysis is listed in Equations (1) to (3), where G is the total plasma glucose, Q is the effect of infused insulin, and I represent plasma insulin. The term p_G and a_G captures patient endogenous glucose removal and insulin-mediated glucose removal saturation parameter, respectively. P represents the glucose appearance rate in plasma from carbohydrate content. EGP_{max} represents the production of maximum endogenous glucose while CNS represents central nervous system (CNS) glucose uptake.

Insulin sensitivity, S_I represents patient-specific insulin-mediated glucose removal, which also indicates evolving patient condition [19,26,27]. Endogenous insulin secretions are I_B and k_I while intravenous insulin administration is u_{ex} [28]. Transport rates and saturation constants are n, k, a_G, a_I, and volumes are V_G, and V_I that have been validated through several studies [29,30].

Using the glucose-insulin system model, patient-specific glycemic response can be generated for time-varying S_I, and hour-to-hour variation as patient condition evolves. The patient-specific profile can be obtained by fitting the model to

retrospective clinical data for blood glucose measurements, insulin and carbohydrate administration input data from the protocols. The resulting insulin sensitivity profile has been validated in correlation to gold standard euglycemic clamp and intravenous glucose tolerance test data [25,31], as well as in silico virtual trials [27,29,32,33].

ii. Sepsis Score

In this study, a well-known sepsis score is calculated following the criteria prepared by the American College of Chest Physicians - Society of Critical Care Medicine (ACCP-SCCM) [5]. This sepsis score was initially created in 2001 during the International Sepsis Definitions Conference. In general, this sepsis score is calculated based on two commonly used criteria, which are SIRS and Sepsis-related Organ Failure (SOFA) [6].

Table 1 shows the sepsis score criteria. Details of the criteria for determining the SIRS and organ failure (OF) scores can be found in Suhaimi et al [28]. Like other scores, this scoring is widely used to represent the complexity level of the syndrome consistently, for evaluation and standardized description. The advantages include a consistent means of allowing clinicians to assess patient condition to guide care [28]. It is normally calculated daily, and uses a hierarchy of criteria defined in Table 1 based on an average of 24 hours of treatment and response to care.

Table 1. Sepsis score criteria

	Score	Infection	SIRS > 2	OF ≥ 1	Fluid resuscitation	Inotrope	High dose inotrope
Normal	0						
Sepsis	1	✓	✓				
Severe sepsis	2	✓	✓	✓	✓		
Septic shock	3	✓	✓	✓	✓	✓	
Refractory septic shock	4	✓	✓	✓	✓	✓	✓

iii. Hourly Scoring Systems (SS_h and SS_{H1})

To obtain a useful score that can be used by a clinician to guide diagnosis and treatment in clinical real-time, defined here as hourly or more frequent for sepsis, the current sepsis score needs to be modified. Figure 1 shows the classification for calculating SS_h, as an hourly scoring system that represent sepsis condition. SS_h is determined by calculating the summation of individual component scores used to calculate the current sepsis score. In contrast, the original sepsis score is determined by following the hierarchy in Table 1.

In Figure 1, each element of A to D has a value of 1 if they are true. For example, at time t, if a patient had SIRS ≥ 2 and had an infection, the score for A will become 1. If the patient had SIRS ≥ 2 but was free from infection, the score for A is 0. Next, if the patient had mild or more severe organ dysfunction or failure, defined by SOFA ≥ 1 for at least one SOFA score component, at time t, B become 1. Otherwise, it is 0. The same method is applied to the criteria C, and D, for fluid resuscitation and inotrope usage, respectively. Finally, the SS_h value is calculated

by summing the values of A, B, C and D, as presented in Equation 4. Therefore, the range of SS_h is 0 to a maximum value of 4.

Importantly, there is no hierarchy involved, which means that if a patient has all the criteria B, C and D, but no SIRS ≥ 2 due to treatment, then they still have a positive score for sepsis. This case would not hold in the original hierarchical definition in Table 1. The difference is that calculated daily, one needs only to have these criteria met daily and the hierarchy is useful. However, hourly assessment of a variable patient does not work well with this hierarchy.

$$SS_h = A + B + C + D \quad (4)$$

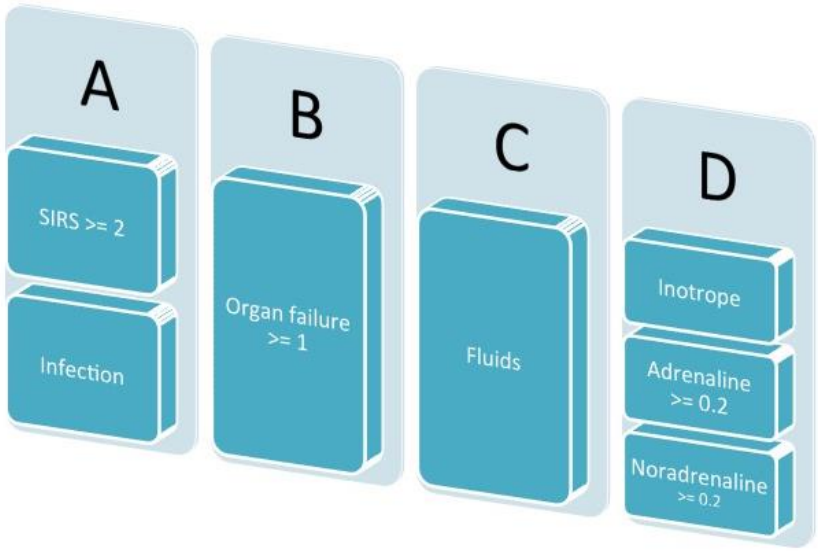

Figure 1. Components for determining an hourly sepsis score, SS_h

Finally, a further modified sepsis score SS_{H1} is introduced. This score is calculated like SS_h in Figure 1. However, it eliminates part of criteria A regarding

SIRS score, since almost all ICU patients meet this condition for many hours of their stay. Hence, it may not add resolution to include this score.

iv. Sepsis Score Analyses

Overall, there are thus two modified sepsis scores to consider, SS_h and SS_{H1}. These are compared to each other, the original unmodified sepsis score, and to insulin sensitivity profiles, level and hourly change in insulin sensitivity. The goal is to determine whether model-based insulin sensitivity profiles can stipulate a valuable additional biomarker or metric to help identify and diagnose sepsis, and at what level of sepsis this outcome might be possible.

v. Patient Data and Retrospective Cohort

A collection of clinical data was obtained from the ICU of Christchurch Hospital, New Zealand. There were a total of 30 patients that had sepsis during their stay and were selected in this study. They were identified by having positive blood culture results and also by a judgment of experienced senior intensive care clinicians. The SIRS score was calculated for every hour for all of the patients. In addition, all other data was collected for each patient and the metabolic treatment data, including insulin and nutrition given and resulting blood glucose measurements, as well as their timing, were collected and used to identify hourly patient specific S_I profile for each patient. Approval by the Upper South Regional Ethics Committee of New Zealand has been obtained for this study and use of the data. The retrospective cohort information including the mortality status is shown in Table 2.

Table 2. Retrospective cohort information

No	Medical Subgroup	Age	Apache II score	Sex	Mortality
1	Pneumonia	71	25	M	
2	Pneumonia	30	10	F	
3	ARDS	63	11	M	
4	Respiratory failure	76	17	M	Y
5	Type 1 DM	46	29	M	Y
6	Type 2 DM	78	19	F	
7	COPD	54	17	M	
8	CAP	88	24	M	Y
9	Sepsis	64	19	F	
10	Gastrectomy	49	12	M	
11	Pneumonia	56	18	M	
12	Sepsis	67	16	F	
13	COPD	55	13	M	
14	Pneumonia	78	15	M	
15	Sepsis	59	29	M	
16	Septic shock	49	19	F	
17	Septic shock	55	17	F	
18	Pneumonia	60	18	F	
19	Otitis	43	18	F	
20	Pneumonia	64	15	M	Y
21	CAP	61	17	F	
22	CAP	74	22	M	
23	Multiple trauma	63	19	F	
24	CAP	52	23	F	
25	Pneumonia	64	20	M	Y
26	CAP	75	23	M	
27	Pneumonia	75	21	M	
28	Pneumonia	70	27	F	
29	GBS	43	8	M	
30	CAP	80	24	M	

a. ARDS - Acute Respiratory Distress Syndrome
b. COPD - Chronic Obstructive Pulmonary Disease
c. CAP - Community Acquired Pneumonia
d. GBS - Guillain-Barré Syndrome

Table 3 summarizes the demographic and baseline criteria of the sepsis cohort, where male and female patients are 18 and 12, respectively. The median age of the cohort is 63 years whereas median [IQR] Apache II score is 19 [16-23]. Total

hours in ICU for the sepsis cohort is 7624 hours, and median length of stay (LOS) is 10.5 days.

Table 3. Demographic and baseline criteria of the sepsis cohort. Median [IQR] is used where appropriate.

Demographic	
Number of patients	30
Percentage of male	60%
Age	63 [54 – 74]
Apache II score	19 [16 – 23]
Total hours in ICU	7624
Length of stay (days)	10.5 [6 – 15]
Baseline criteria	
Temperature (°C)	36.6 [36.0 – 37.6]
Heart rate (beats/min)	97 [87 – 110]
Mean arterial pressure (mmHg)	73 [67 – 83]
White cell count (per Liter)	11.6 [7.9 – 20.4]
Partial pressure of carbon dioxide (mmHg)	47.5 [39.0 – 58.0]
Partial pressure of oxygen (mmHg)	90 [72 – 113]

Results and Discussion

i. Insulin sensitivity profile of the sepsis cohort

Identified insulin sensitivity profiles, $S_I(t)$, for all 30 patients provide an hour-to-hour trajectory for each patient, before, during and after sepsis. Figure 2 illustrates the per-patient cumulative distribution functions (CDFs) of S_I for all 30 patients, where the shaded area indicates the 5th to 95th percentile patients and the dotted line represents the median patient, with the 25th and 75th percentile patients also shown. It is clear that there is significant inter-patient and intra-patient variability in S_I. Figure 2 also presents similar data in a box plot for each patient.

Table 4 presents the S_I results, hourly change in insulin sensitivity (ΔS_I) and percentage of changes in insulin sensitivity ($\%\Delta S_I$) across patients and cohort. Maximum S_I values are highly variable across patients. The highest S_I value in the cohort is 9.2734e-3 L/mU.min, in Patient 24. Median S_I and median ΔS_I of the cohort is 0.4193e-3 and 0.004253e-3 L/mU.min, respectively, where the latter value very near to 0 indicates that the median hour-to-hour change is no change in insulin sensitivity, matching prior reports [27]. This value also indicates that a sepsis patient, or post-sepsis patient, is equally likely to have a rise or fall in insulin sensitivity hour-to-hour, with no bias in direction of the change, although there is significant inter-patient variability seen in Table 3 when examining individual patient results.

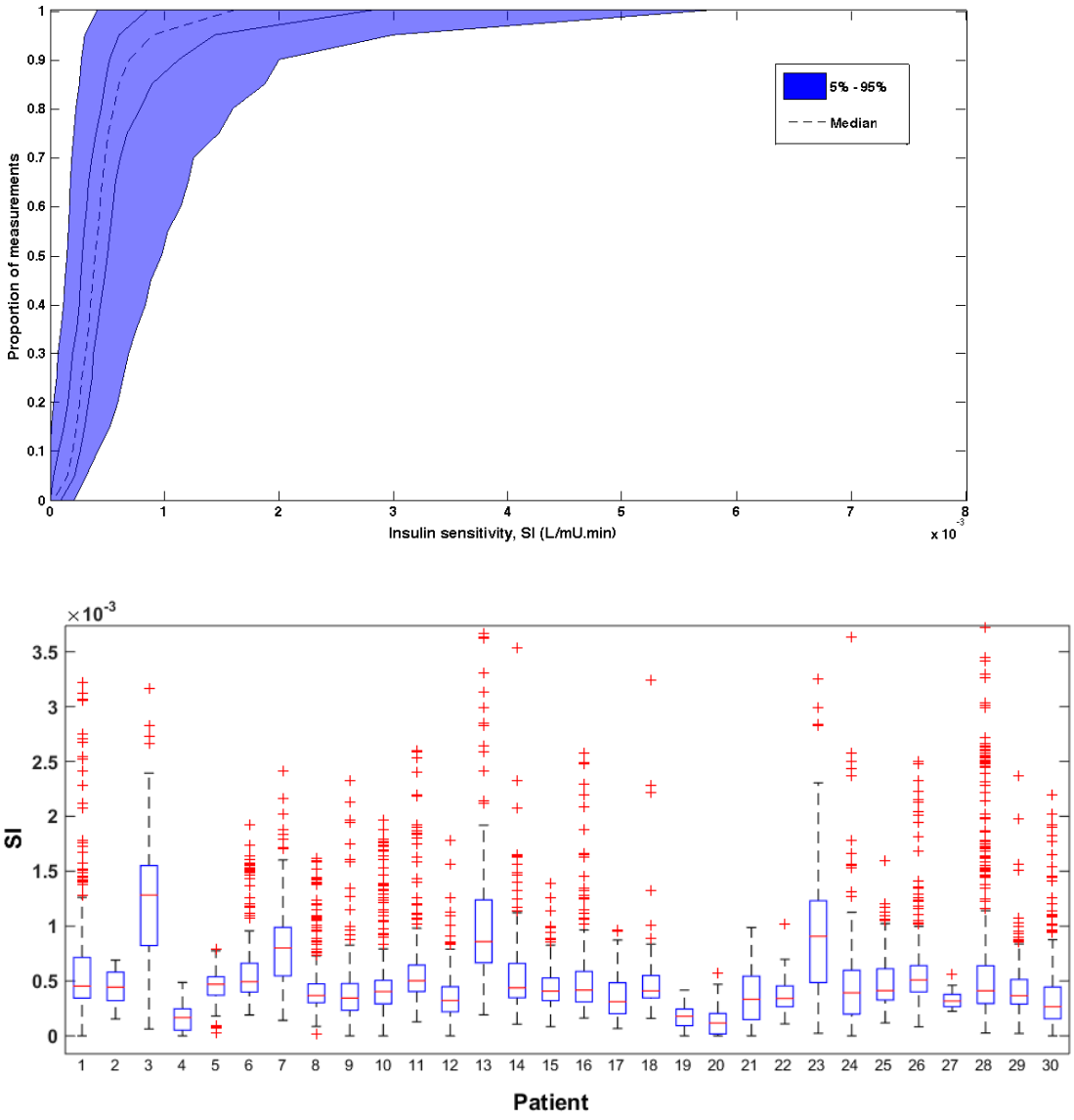

Figure 2. Top: Per-patient insulin sensitivity CDFs for all 30 patients, shown as median, IQR and 5th – 95th percentile patients. Bottom: the same data shown per-patient as a box-plot

Table 4. Median insulin sensitivity, minimum and maximum insulin sensitivity, and median changes in insulin sensitivity among 30 patients in the sepsis cohort

No	Median S_I (10^{-4})	Minimum S_I (10^{-4})	Maximum S_I (10^{-4})	Median ΔS_I (10^{-6})	Median ΔS_I (%)
1	4.527	0.001	32.155	3.711	1.084
2	4.433	1.540	6.897	-7.010	-1.261
3	12.827	0.625	31.657	4.068	0.471
4	1.657	0.001	4.870	5.307	3.349
5	4.702	0.325	7.906	-1.072	-1.021
6	4.927	1.900	19.234	2.825	0.562
7	8.011	1.410	24.177	-1.676	-0.255
8	3.674	0.114	16.201	6.680	1.531
9	3.439	0.001	23.290	4.637	1.255
10	4.026	0.001	19.655	5.655	1.597
11	5.017	1.282	58.959	7.949	1.819
12	3.223	0.001	17.804	7.216	1.967
13	8.588	1.917	42.527	0.072	0.012
14	4.379	1.062	35.339	-0.020	-0.004
15	4.077	0.846	13.840	9.327	2.705
16	4.176	1.623	25.738	1.969	0.573
17	3.119	0.670	9.691	7.596	3.226
18	4.101	1.589	66.076	0.097	0.003
19	1.786	0.001	4.169	2.862	1.118
20	1.171	0.001	5.768	6.515	4.243
21	3.337	0.001	9.867	20.923	4.554
22	3.400	1.089	10.220	8.619	2.053
23	9.070	0.230	32.530	48.204	5.682
24	3.920	0.001	92.734	17.926	7.999
25	4.119	1.182	15.956	3.845	0.972
26	5.093	0.830	25.005	2.852	0.883
27	3.173	2.241	5.589	-20.532	-6.079
28	4.103	0.263	74.211	7.589	0.845
29	3.667	0.217	23.730	2.151	0.460
30	2.653	0.001	21.980	3.381	1.132
Cohort	**4.193**	**0.001**	**92.734**	**4.253**	**1.114**

Figure 3 shows the 5th - 95th percentile, IQR (75% and 25%) and median (50%) for the hour-to-hour stochastic model created from the 30 patients based on the models developed by Lin et al. [27,34]. The variation distributions are plotted as

$S_{I\ (n+1)}$ against S_{In} on the y-axis and the x-axis, respectively. The distribution indicates the hour-to-hour patient metabolic variability in S_I.

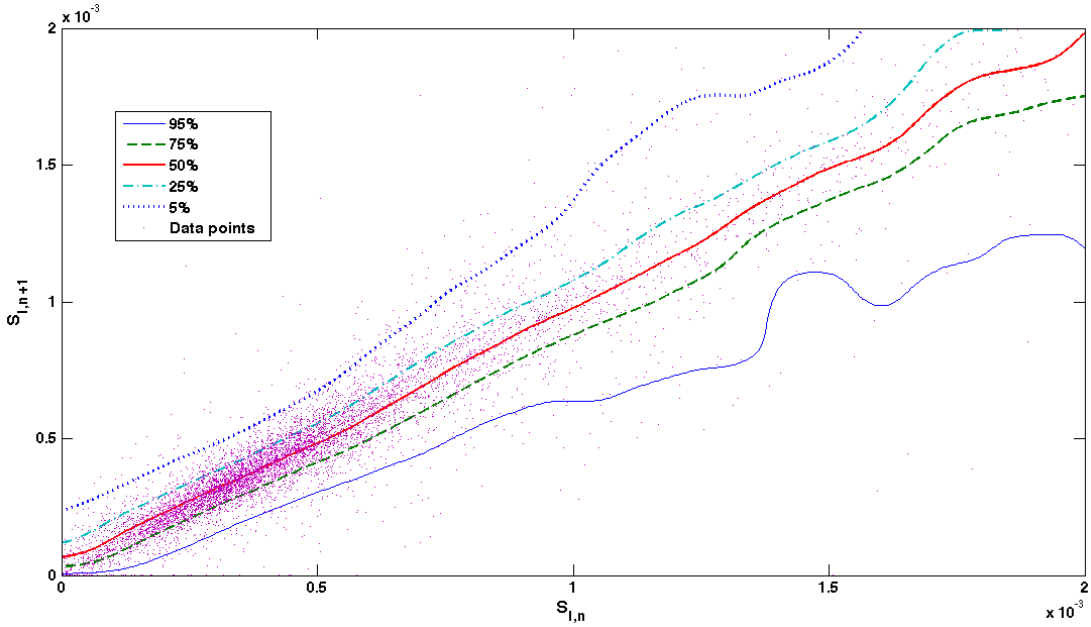

Figure 3. Hourly insulin sensitivity distribution of the sepsis cohort

ii. Unmodified sepsis score analysis

Figure 4 shows the hourly distribution of sepsis score for the whole length of stay for two patients randomly selected from the sepsis cohort. In Figure 4, the score of Patient 22 changes effectively instantly, with a difference of two levels of sepsis score, as seen at minutes 1620 to 2160. Additionally, it can be observed that the sepsis score is highly variable between a score of 0 and 1 for most of the stay of Patient 24. These plots suggest that sepsis scores calculated daily do not capture the true state of sepsis, SIRS and infection in hourly measurement, which cannot change to two or even three stages at this fast. Instead, it shows how the hierarchical, unmodified sepsis score cannot be used hourly without the proposed modifications in Figure 1.

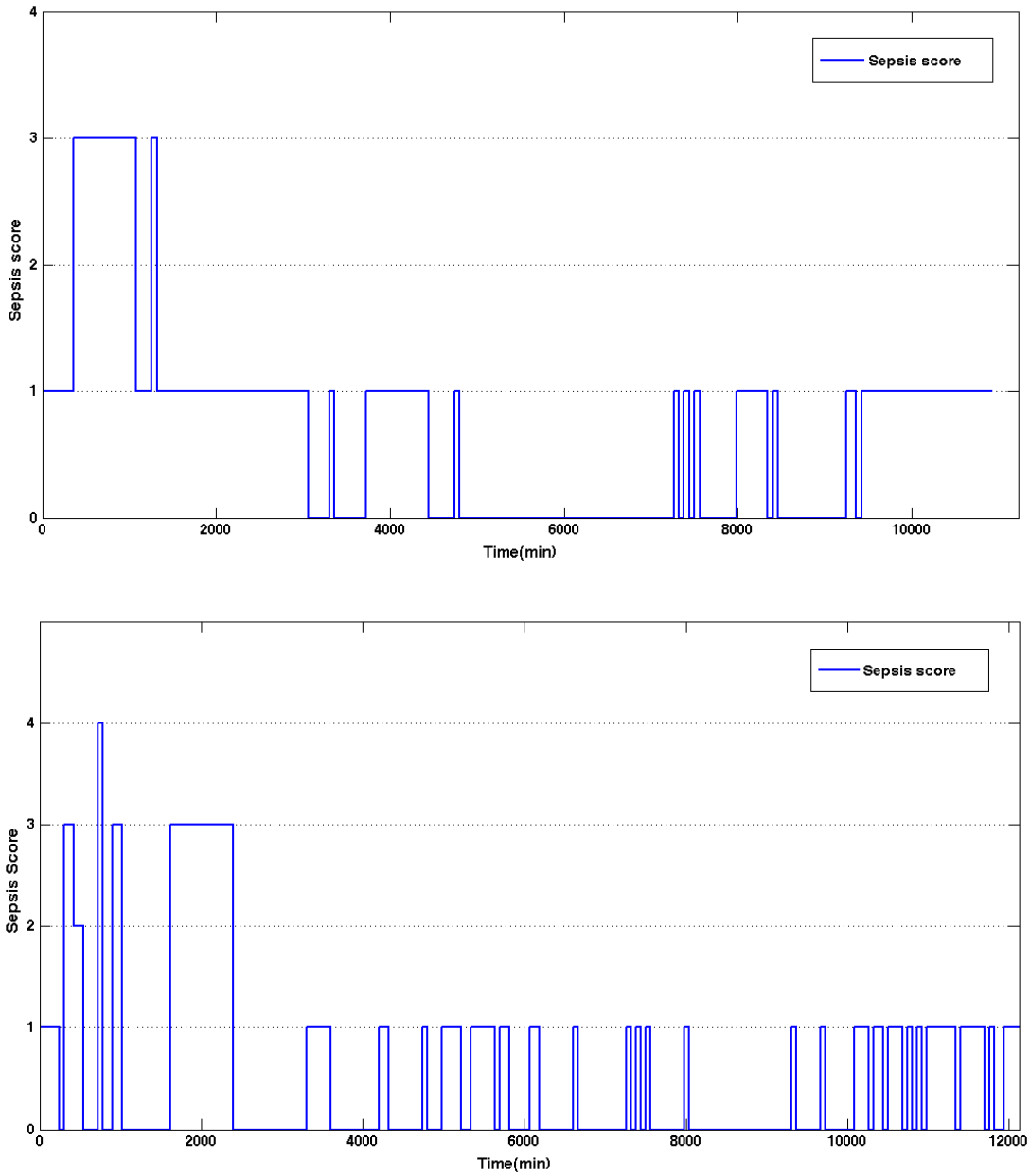

Figure 4. Hourly plot of the unmodified sepsis score for Patients 22 (top) and 24 (bottom)

iii. Hourly sepsis score (SS_h) of the sepsis cohort

Figure 5 illustrates SS_h for all 30 patients during their whole stay in ICU. Overall, there were a total of 7624 hours of treatment where patients had SS_h = 2 for the most hours (43%). There were 25.9%, 9.8% and 2.6% of hours where patients had SS_h scores of 1, 3 and 4, respectively. The remaining 18.7% of the total hours are where patients had SS_h = 0.

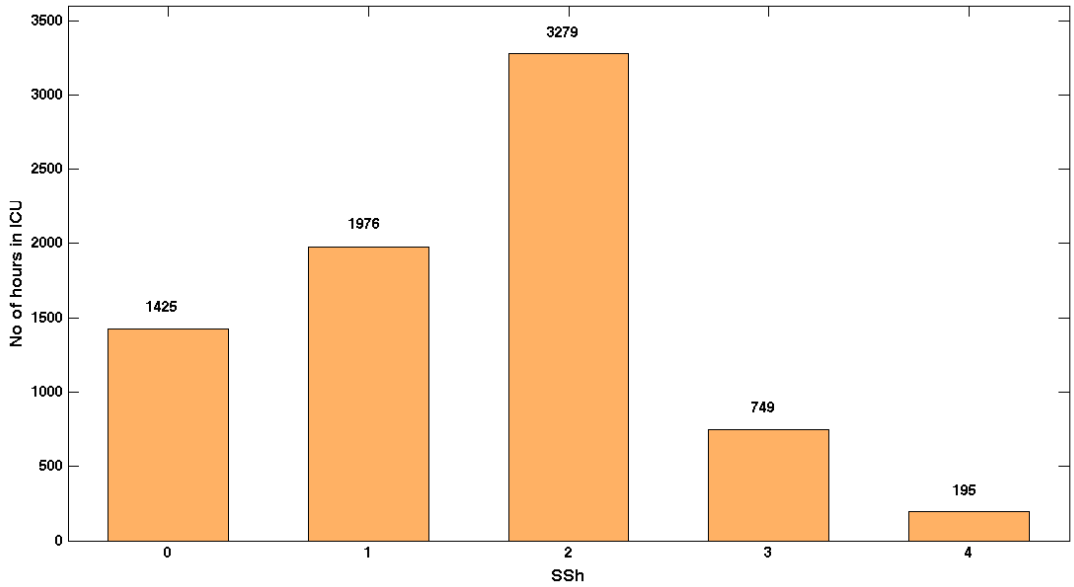

Figure 5. Cumulative hours of SS_h for 30 patients in the sepsis cohort during their stay in ICU

Figure 6 shows the hourly distribution of the modified sepsis score, SS_h, and insulin sensitivity for the entire stay of the Patient 3 and Patient 24. The right panel of y-axes represents SS_h and left panel of y-axes represents the insulin sensitivity value. Patient 3 had a higher score with a fluctuating score during the second half of the stay as compared to the original, unmodified sepsis score in Figure 4. In Figure 6, the SS_h of Patient 24 is also highly variable, unlike the plot of the original sepsis score.

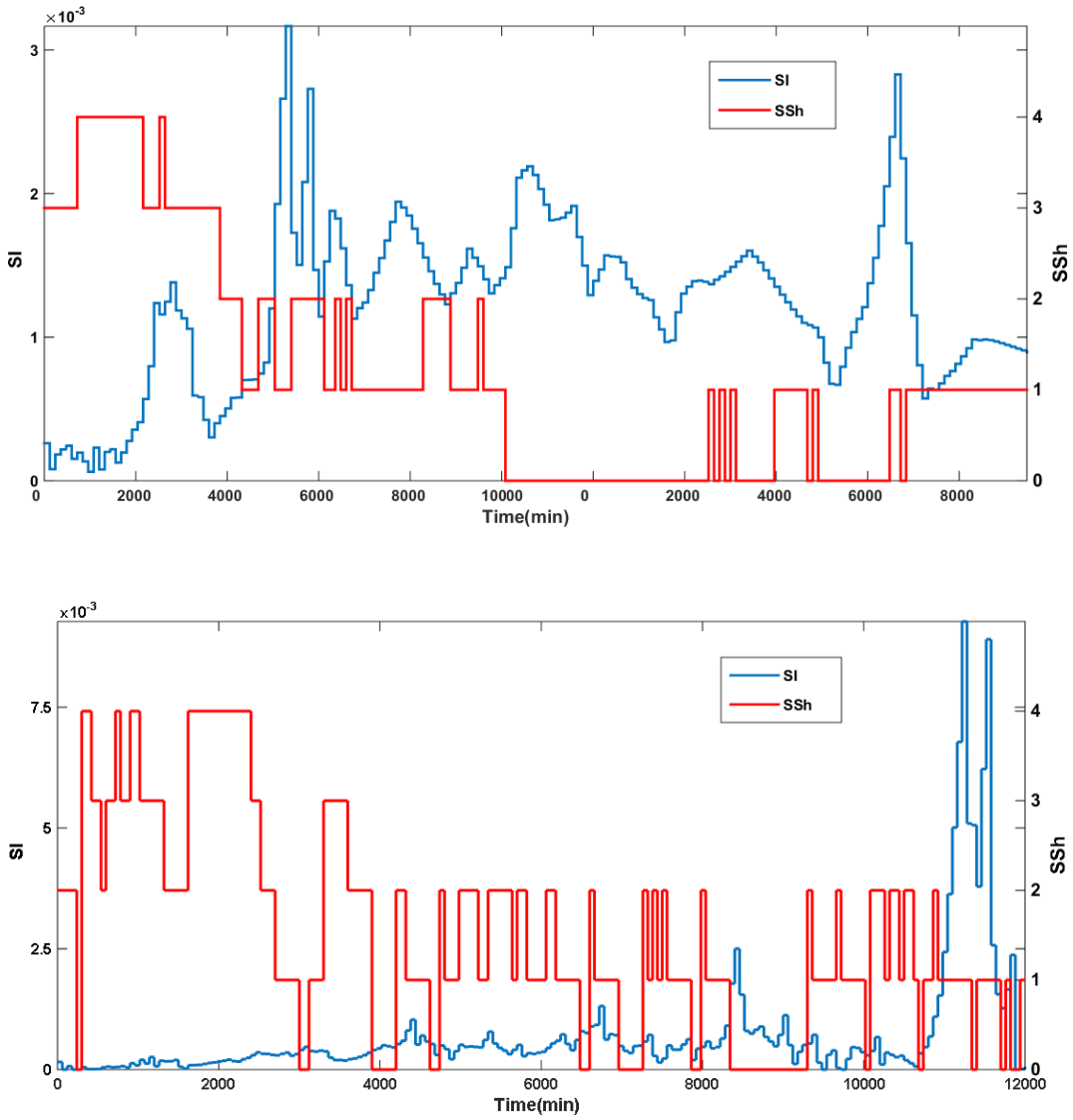

Figure 6. Hourly plot of SS_h and SI for Patient 3 (top) and Patient 24 (bottom)

Figure 7 represents the cumulative data points of A, B, C and D when $SS_h = 1$. There was 1976 measurement of $SS_h = 1$ during the stay for all 30 patients in the cohort. A has the highest frequency followed by B, D and C. In Figure 7, criteria A dominates the total measurement of SS_h at score 1 with a 56% (1086) of total measurements, reflecting the influence of SIRS score and how it is endemic to almost all ICU patients even without sepsis. Criteria B recorded the second

greatest with a total of 690 measurements, followed by D and C with 104 and 96, respectively.

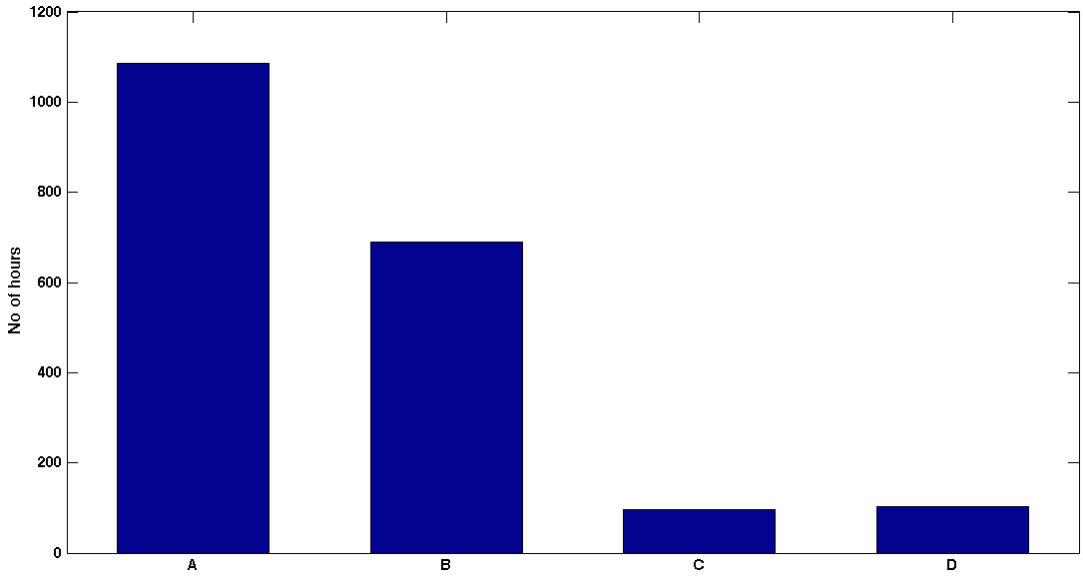

Figure 7. Comparison of score A, B, C and D components for SS_h

iv. Modified hourly sepsis score (SS_{H1})

SS_h in Figure 6 can still be unstable for the hourly assessment of sepsis condition due to high fluctuation seen in the per-patient plots, due primarily to the influence of SIRS score, which adds extra effective noise. SS_{H1} provides a more comprehensive and stable score with maximum and minimum values of 3 and 0, respectively. Figure 8 shows the hourly distribution of insulin sensitivity, S_I, changes in insulin sensitivity (ΔS_I), percentage of changes in insulin sensitivity ($\%\Delta S_I$) and SS_{h1} for Patient 3 and Patient 24.

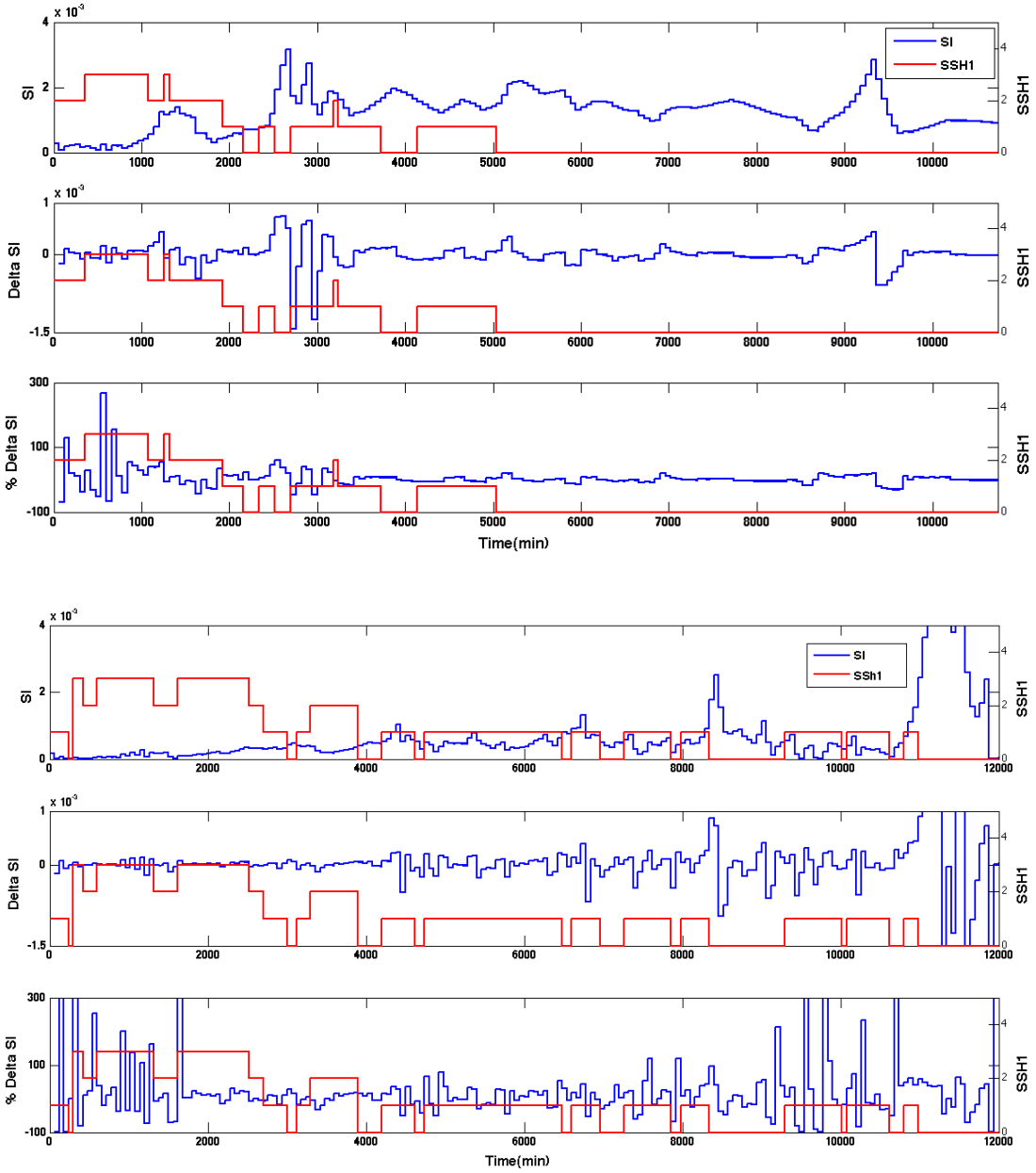

Figure 8. Hourly plot of S_I, ΔS_I, $\%\Delta S_I$ and SS_{H1} for Patient 3 (top) and Patient 24 (bottom)

It is clear in Figure 8 that there is a stronger correlation between insulin sensitivity and the modified hour sepsis score, SS_{H1}. In general as sepsis declines patient-specific insulin sensitivity tends to rise and become more variable as condition improves. Thus, rising insulin sensitivity and increasing variability (ΔS_I) would be hypothesized to be markers of improving condition from sepsis, and vice versa for its diagnosis.

Figure 9 presents the receiver operating characteristic (ROC) plot. X-axis in Figure 9 represents (1-specificity) while y-axis represents sensitivity. Plotted lines lay in a sequence according to the SS_{H1} value. As expected, higher SS_{H1} values ($SS_{H1} \geq 3$), for greater levels of sepsis, yield the best possible prediction using insulin sensitivity level alone, and the plots show a similar trend for all categories of SS_{H1}. There is a small gap between $SS_{H1} \geq 1$ and $SS_{H1} \geq 2$, and a large gap has been observed between $SS_{H1} \geq 3$ to the rest indicating it is more diagnostic for severe sepsis.

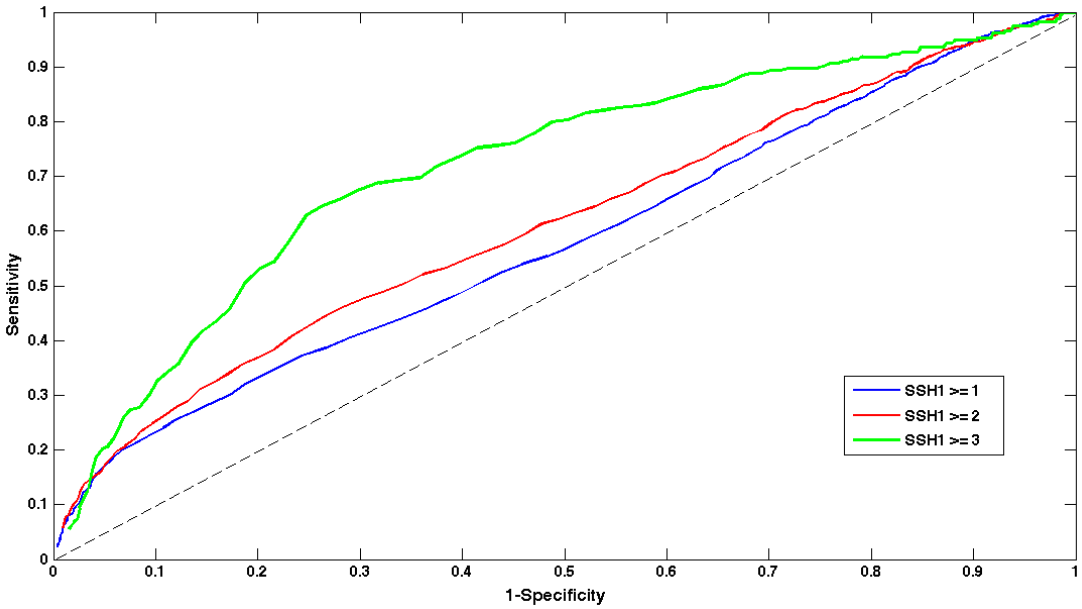

Figure 9. Receiver operating characteristic (ROC) plot showing the sensitivity and specificity relation of SS_{H1} and insulin sensitivity

Figure 10 shows the CDFs of S_I on the SS_{H1} score basis. $SS_{H1} = 0$ has the highest S_I distribution followed by patients with $SS_{H1} = 1$, $SS_{H1} = 2$ and $SS_{H1} = 3$. However, the S_I distribution for $SS_{H1} = 0$, 1 and 2 are almost overlaid. S_I reduces as the

patient condition worsens, as hypothesized. However, the discrimination, while significant ($p<0.05$), is not large and there is significant overlap that affects diagnostic value as seen in Figure 9 for these two levels. The p-values computed using Mann-Whitney test are shown in Figure 10. P-values are 0.6742 ($SS_{H1} = 0$, $SS_{H1} = 1$), 0.0392 ($SS_{H1} = 0$, $SS_{H1} = 2$), 0.3337 ($SS_{H1} = 0$, $SS_{H1} = 3$), 0.0581 ($SS_{H1} = 1$, $SS_{H1} = 2$), 0.4059 ($SS_{H1} = 1$, $SS_{H1} = 3$), and 0.8379 ($SS_{H1} = 2$, $SS_{H1} = 3$), respectively. The clearer difference when $SS_{H1} = 3$, the most severe septic state, shows more diagnostic potential and also reflects the ROC curve in Figure 9.

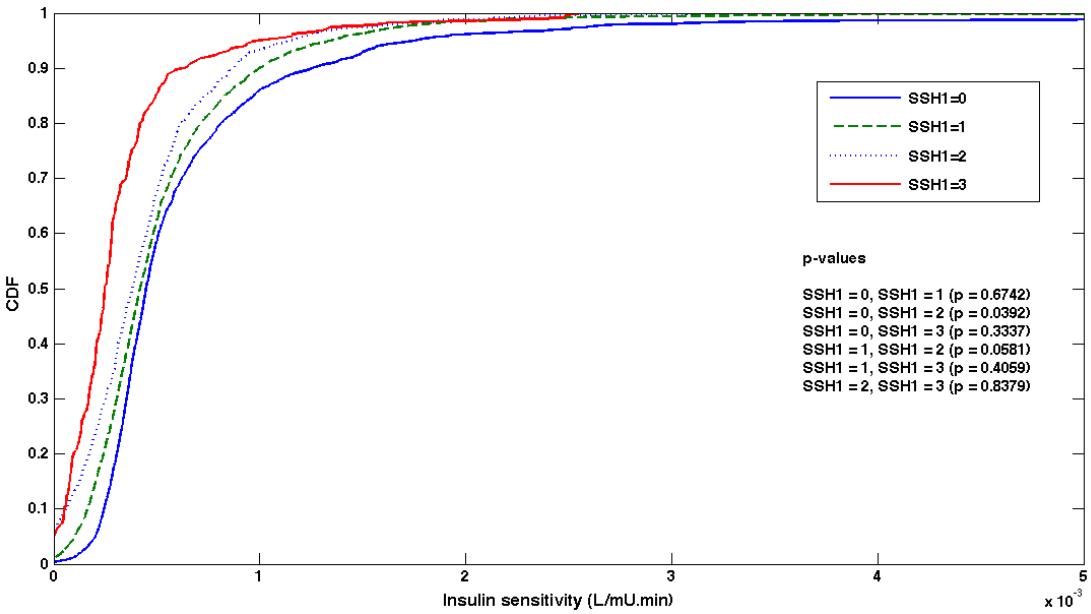

Figure 10. Cumulative distribution functions of insulin sensitivity grouped by SS_{h1}.

Insulin sensitivity profile provides important information on the metabolic status of any particular patient. In this study, insulin sensitivity distributions are very similar among the sepsis patients in the cohort as seen in Figure 3. Most of the patients in the cohort had a similar S_I distribution.

The dynamic change in S_I from hour-to-hour also provides information on metabolic dynamics and insulin resistance in this cohort. Importantly, the variability of S_I over the next hour is highly relying on its current value. Therefore, the stochastic model in Figure 3 represents the S_I transition from one hour to the next and changes in variability may be indicative of changes in patient condition, creating a further potential biomarker. Moreover, S_I and change in S_I offer a further diagnostic value particularly at certain thresholds.

Overall, from the whole length of stay for this sepsis cohort, the standard sepsis scores are fluctuating. Generally, the sepsis and infection condition of a patient would not change this fast. By definition, sepsis exists by the presence of SIRS and infection. However, the frequent change in Figure 4 suggests a failure of the score hierarchy typically used on a daily basis that takes the average or worst case of over the day. This result may not be surprising since SIRS symptoms are treated, such as high temperature, thus negating the entire hierarchy if the SIRS criteria is not met. Hence, the SIRS score was used and excluded in the modified SS_h and SS_{H1} scores, respectively analyzed here, which are calculated hourly and thus do not use the hierarchical scoring method used daily.

From the plots in Figure 6, it can be concluded that SS_h makes an improvement but not all non-physiological fluctuation is eliminated. Since SS_h is calculated based on each component in determining the original sepsis score without a hierarchy, the score can be due to any set of criteria. It is thus more representative of true condition, but biased by the fluctuations in SIRS scores, which are endemic to all ICU patients and not just in sepsis. In particular, the

high frequency of criteria A in Figure 7 showed that SIRS is a leading contributing factor in developing the SS_h score, with more than 50% of the total score. These results thus justified the choice to also consider a sepsis score without SIRS criteria, SS_{h1}, for analysis versus insulin sensitivity and its hour-to-hour evolution.

Overall, Figure 8 implies that SS_{H1} decreases with increases in insulin sensitivity, given that S_I is above a certain threshold. However, patients might have different patient-specific thresholds or baseline values to indicate changes in their metabolic condition. Similarly, changes in S_I may also vary between patients. Some patients may have a huge change in S_I when shifting metabolic condition, while others may experience much smaller changes for the same event.

Nevertheless, ΔS_I and $\% \Delta S_I$ do not show a significant correlation to the SS_{H1} and thus may not add much as a biomarker. Equally, these results show that S_I is an effective marker, but that patient-specific thresholds would be needed to make automated diagnosis possible without additional, external data. In particular, the relation of insulin sensitivity, S_I to SS_{H1} may suggest S_I as a significant marker in determining severe sepsis levels in critical illness.

Hence, the ability to delivery very early diagnosis is unclear, but the negative predictive value of this marker alone is significant. Positive prediction of lower sepsis scores will require more information. These results are mainly due to the fact that S_I lags condition, resulting in S_I values that do not match SS_{H1} score

when sepsis state is changing. The result is a loss of diagnostic power largely due to the hourly nature of assessment and this lag.

Conclusions

Identification of an inflammatory response to infection at an early stage would enhance the understanding and knowledge of cellular and immunology aspects that may cause sepsis, as well as aid decisions to give aggressive care to reduce mortality and morbidity. Currently, early detection and treatment is very challenging due to the lack of physiological information accessible in real-time that is relevant to infection, organ failure and sepsis. This study shows that model-based metabolic information on insulin sensitivity, S_I, can be highly related to SS_{H1}, a specifically modified hourly sepsis scoring system indicating sepsis degree. Importantly, it shows that S_I decreases with worsening condition and increases with improvement in patient condition, which is similar to some previous studies [16,17,19,20]. However, information on S_I is insufficient to determine the exact sepsis condition of a patient particularly at moderate sepsis levels (e.g., $SS_{H1} = 1$), which are important for early diagnosis as the condition develops. Hence, the main contributions of this work are to develop a modified clinical sepsis score that can be effectively used hourly for real-time diagnosis and monitoring (SS_{H1}) and to show that the impact of sepsis on metabolic markers, like S_I, is clear, providing an avenue for further study and development of easily automated, model-based markers for diagnosis of sepsis.

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Conflict of Interest

All the authors would like to declare that there is no conflict of interests.

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