# Assessing the risk of DIC development in sepsis and SIRS

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## Abstract

Disseminated intravascular coagulation (DIC) is characterized by a systemic activation of the blood coagulation system, leading to clot formation, blood vessel obstruction and organ dysfunction. Substantial consumption of platelets and coagulation factors in this process may in turn cause bleeding, which further decreases the patient's chances of survival [1]. Between 30% and 50% of sepsis patients develop DIC. Several diagnostic scores based on general coagulation tests such as prothrombin time (PT), fibrinogen, d-dimer and platelet counts are in use to objectify the subjective clinical diagnosis of DIC based on clinical signs and symptoms [2, 3]. However, these scores are unsuitable to assess the risk of DIC in sepsis patients, to support the decision whether to initiate anticoagulant therapy to mitigate this risk.

We developed a method to assess the risk of developing DIC for patients with SIRS or sepsis, 24 hours in advance. For this we selected 3606 SIRS and sepsis patients from the Philips eICU Research Institute database (2277 were included in a training- (1082 DIC cases) and 1329 in a test set (519 DIC cases)). We used a logistic function to select single biomarkers, statistical features extracted from vital sign dynamics, patient characteristics or the Apache II score that estimate the probability of DIC with an AUC > 0.55 in the training set. Minimum sets of these features were then combined in a logistic model. A combination of lactate, total bilirubin and respiration energy predicted DIC with an AUC of 0.85 in the test set.

Our model provides a clinically applicable method to identify sepsis/SIRS patients with a high probability to develop DIC.

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## Introduction

Disseminated intravascular coagulation (DIC) is characterized by a systemic activation of the blood coagulation system, leading to clot formation, blood vessel obstruction and organ dysfunction. Substantial consumption of platelets and coagulation factors in this process may in turn cause bleeding, which further decreases the patient's chances of survival [1]. Between 30% and 50% of sepsis patients develop DIC. Several diagnostic scores based on general coagulation tests such as prothrombin time (PT), fibrinogen, d-dimer and platelet counts are in use to objectify the subjective clinical diagnosis of DIC based on clinical signs and symptoms [2, 3]. However, these scores are unsuitable to assess the risk of DIC in sepsis patients, to support the decision whether to initiate anticoagulant therapy to mitigate this risk.
We developed a method to assess the risk of developing DIC for patients with SIRS or sepsis, 24 hours in advance.

## Materials & Methods

We selected 3606 patients with a diagnosis of SIRS or sepsis from the Philips eICU Research Institute database (ICD9 codes starting with 995.9). This data set was divided into a training set of 2277 patients (1082 DIC cases and 1195 controls) and a test set of 1329 patients (519 DIC cases and 810 controls).
DIC was identified by the presence of the IC9 code 286.6 or the availability or possibility to calculate the ISTH DIC score. As measurements for fibrinogen and especially D-dimer/Fibrin Degradation Products were often lacking, we used a total score of 4 instead of 5 as diagnostic for DIC.
We used patient characteristics, vitals signs and laboratory markers in our analyses. Clear outliers were removed. The vital signs (respiration, heart rate and oxygen saturation) were segmented using a sliding window with a length of 120- and an overlap of 60 minutes.

The average, standard deviation, kurtosis, skewness, quantiles 0.25, 0.50, 0.75, range and energy were extracted from each window. Features with more than 50% missing values were excluded from the analysis. The remaining features were Z-score transformed and missing values were substituted by a random number between 0 and 1.

## Results

All the measurements of interest were available for only very few patients, e.g. for some patients only lactate or bilirubin was measured, for others only vital signs were available. To mitigate this problem, we trained logistic regression models for each of the 39 selected measurements and vital signs features separately, in 10-fold cross-validation on the training set. The 21 features that achieved an AUC above 0.55 were used for the development of the DIC risk assessment models.

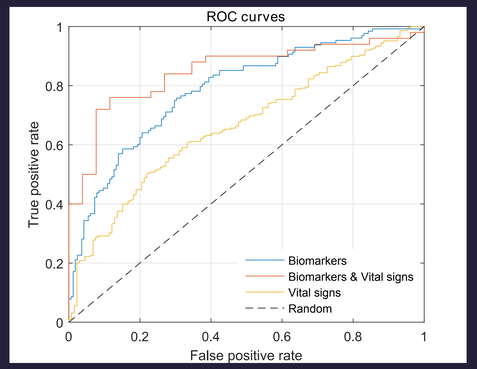


Figure 1: ROC curves for the best performing ensembled classifiers

In order to select the optimal set of measurements included in the ensembled classifier, the performance of different measurement combinations were evaluated. For this we combined the single feature logistic regression models' outputs based on a weighted average proportional to the classifier accuracy calculated on the training set. To reduce the number of model combinations, we only used sets of three models. We computed the best performing combinations when using only vital signs, only biomarkers and a combination thereof (Figure 1, Table 1).

## Discussion

With this study we demonstrate that it is feasible to assess the risk of developing DIC in septic patients well in advance, and with a very limited number of widely available laboratory tests and vital sign measurements. We envision a clinical implementation of our finding whereby the vital sign features, with a high sensitivity and a low specificity, are used for the continuous monitoring of sepsis patients, and trigger further, more specific laboratory tests for a definitive risk assessment when needed.

While our ensemble classifier performs already quite well, we see ample room for improvement. To enable the development of more powerful classifiers, more complete, possibly prospectively collected data sets will be needed.

| | Models for: | Se | Sp | AUC |
|---|---|---|---|---|
| Laboratory tests | Creatinine<br>Lactate<br>Total bilirubin | 58% | 85% | 0.79 |
| Vital sign features | SaO2.std<br>Heart_rate.quant25<br>SaO2.k | 100% | 4.6% | 0.66 |
| Lab tests & vital sign features | Lactate<br>Total bilirubin<br>Respiration energy | 86% | 65% | 0.85 |

Table 1: Performance of the best performing combinations of sets of 3 models consisting of only biomarkers, only vital signs and a combination thereof.
*std: standard deviation, k: kurtosis, quant25: quantile 0.25*

## Conclusion

Our model provides a clinically applicable method to identify sepsis/SIRS patients with a high probability to develop DIC well in advance.

## References

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