

Predicting antimicrobial resistance in Gram-negative bacterial bloodstream infections through evaluation of dynamic host responses and deep learning

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Background

Effective management of bacterial bloodstream infection requires early, appropriate empirical antimicrobial therapy. Antimicrobial resistance is a major contributor to poor clinical response but can be challenging to ascertain because of limitations in turnaround time and sensitivity of culture-based diagnostics. We examined whether host response information during the early phase of treatment could predict antimicrobial susceptibility in Gram-negative bacteria bloodstream infections (GNBSI).

Methods

We analysed data from 2,188 confirmed cases of GNBSI at Imperial College Healthcare NHS Trust in London, UK, between January 2021 and May 2023. We extracted blood biomarkers, demographics, and vital signs within a 60-hour window post-blood culture acquisition. Resistant was defined for aminoglycosides or carbapenems if prescribed empirically without concurrent susceptible antibiotics. Generalized Estimating Equation (GEE) methods were used to analyse the association between features and resistance. For prediction models, time series deep learning using Long-Short Term Memory (LSTM) models were used. To mitigate selection bias, features were normalised relative to the time of blood culture acquisition, focusing only on relative changes in features. The dataset was split randomly, with 80% (n=1,750) used for training and prospective evaluation against an independent holdout set (n=438). Five-fold cross-validation and post-hoc methods for interpretability were applied.

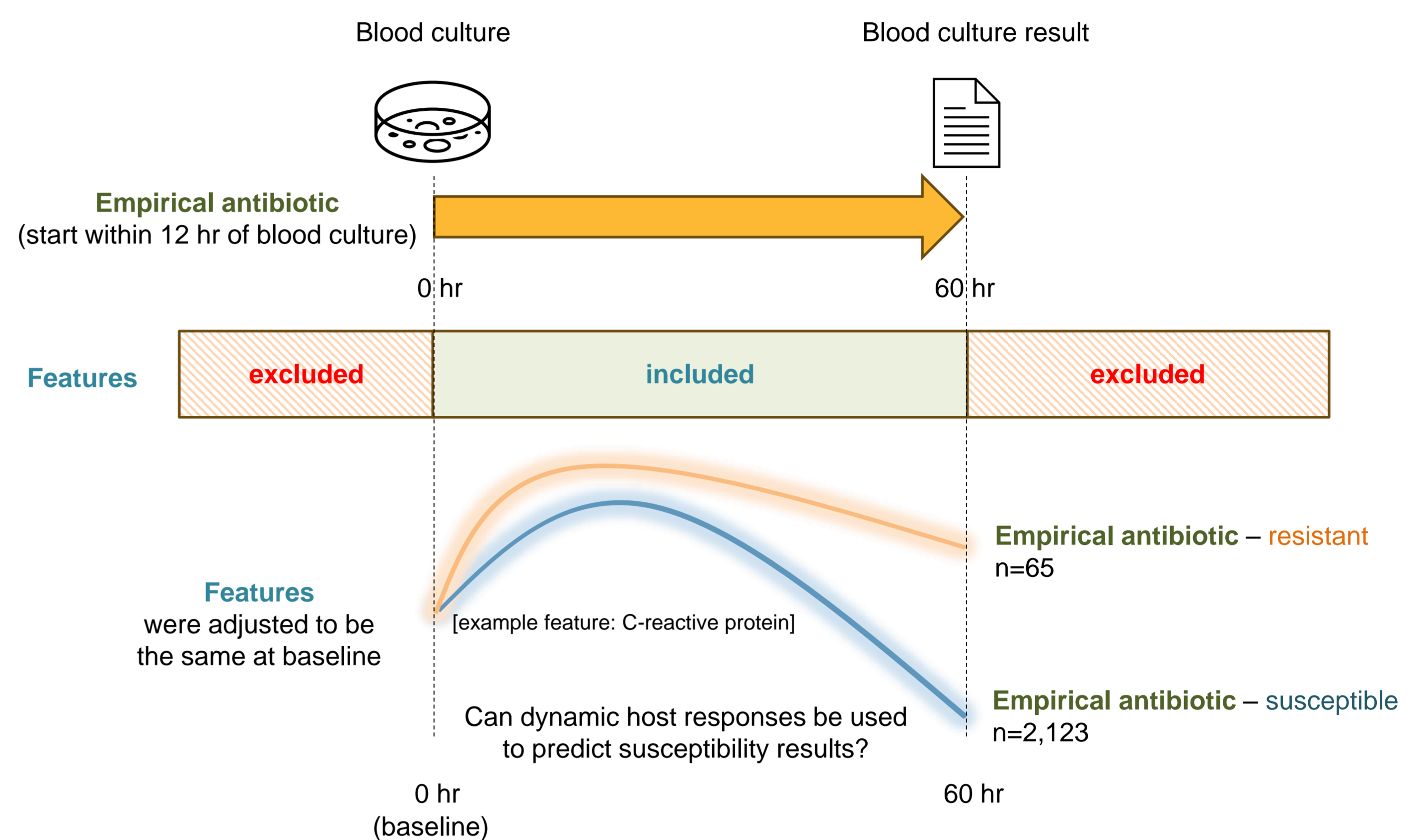
Results

There were 7.9% (173/2,188) and 1.6% (36/2,188) GNBSI instances which were resistant to the aminoglycosides and carbapenems prescribed, respectively. Excluding instances with concurrent susceptible antibiotics, 65 cases were categorised as resistant. After the onset of GNBSI, patients with a resistant isolate had significantly higher C-reactive protein (CRP) (p=0.002), lower temperature (p=0.031), and lower blood pressure (p=0.041). The area under receiver operator curve (AUROC) for the validation set through the LSTM model was 0.73 (IQR 0.69-0.76). Hold out set performance were AUROC of 0.83 (95%CI: 0.71-0.93) with NPV of 0.99, sensitivity of 0.69, and specificity of 0.76. Dynamics of CRP, blood pressure, and temperature over the 60-hour period were the most important features for model prediction.

Conclusions

Use of dynamic host responses to antibiotics shows promise for improving antimicrobial prescribing. With a larger training set, this model has the potential to enhance antimicrobial optimisation in sepsis, particularly in cases of culture-negative infections or when susceptibility information is unavailable.

Study methodology



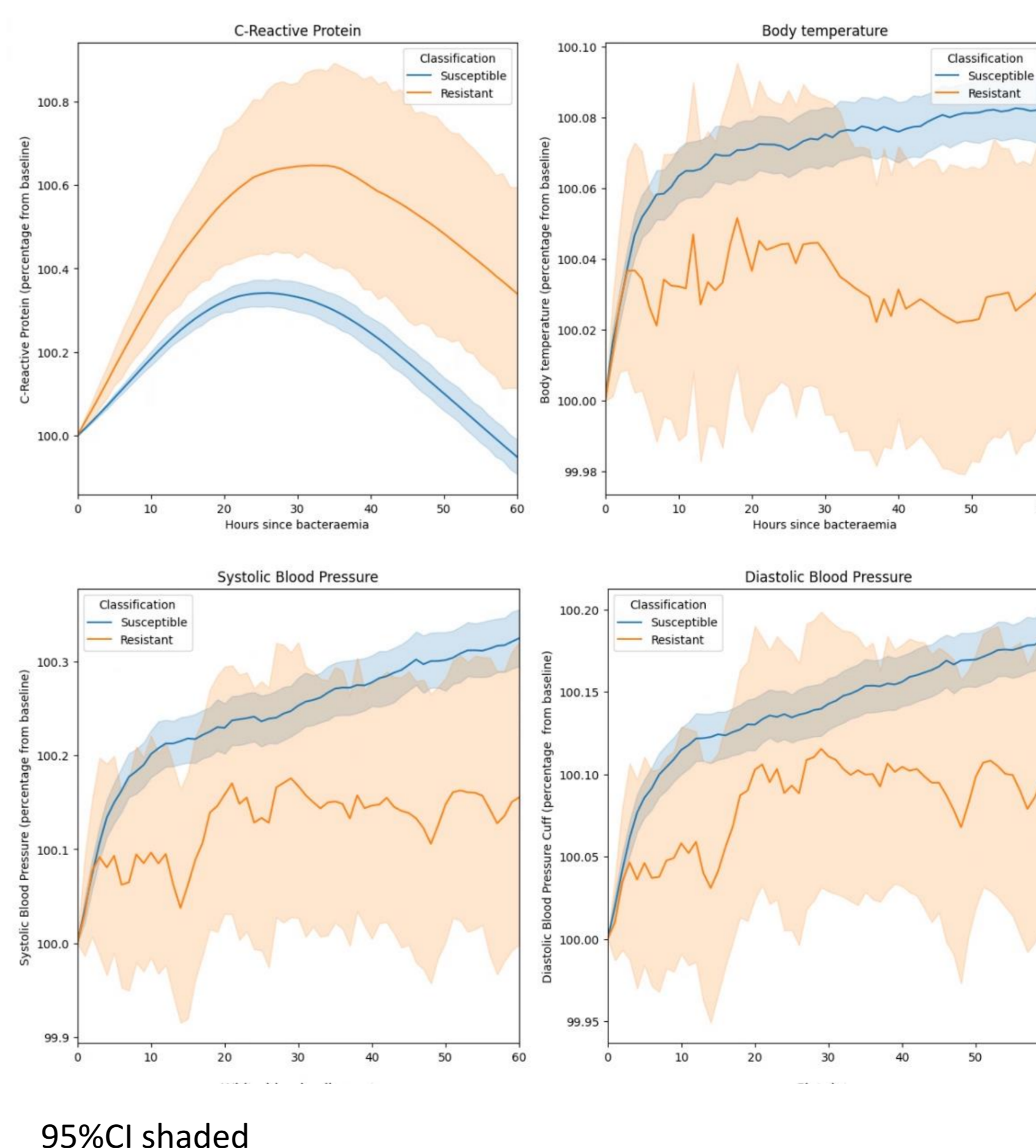
Generalized estimating equation analysis

the associations between percentage change of each feature from the baseline and resistant results

Feature	Intercept (95%CI)	p value	Resistant (95%CI)	p value
C-Reactive Protein	0.203 (0.173 - 0.234)	<0.0001	0.287 (0.104 - 0.470)	0.0021*
Temperature	0.069 (0.061 - 0.077)	<0.0001	-0.043 (-0.082 - -0.004)	0.0312*
Systolic Blood Pressure	0.238 (0.219 - 0.263)	<0.0001	-0.133 (-0.260 - -0.006)	0.0406*
Diastolic Blood Pressure	0.135 (0.120 - 0.150)	<0.0001	-0.070 (-0.144 - 0.004)	0.0628
Respiratory Rate	0.033 (0.029 - 0.038)	<0.0001	-0.021 (-0.043 - 0.002)	0.0691

* statistically significant

Dynamic changes of the selected features over 60-hour period between the two groups



Time series plot

C-reactive protein and their values (blue-red gradient), SHAP values (y-axis), and timesteps in hours (x-axis)

