A validated model for early prediction of group A streptococcal aetiology in necrotising soft tissue infections using minimal patient data

Additional Material

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Supplementary Note 1

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Supplementary Note 2

Dutch Centres of investigation (Validation cohort)

		Location	Academic	Burn centre
1	Amsterdam UMC loc. VUmc	Amsterdam	Yes	No
2	Amsterdam UMC loc. AMC	Amsterrdam	Yes	No
3	LUMC	Leiden	Yes	No
4	Erasmus MC	Rotterdam	Yes	No
5	Red Cross Hospital	Beverwijk	No	Yes
6	Maasstad Hospital	Rotterdam	No	Yes
7	Martini Hospital	Groningen	No	Yes
8	Noordwest Ziekenhuisgroep	Alkmaar	No	No
9	OLVG	Amsterdam	No	No
10	Spaarne Gasthuis	Hoofddorp	No	No
11	BovenIJ ziekenhuis	Amsterdam	No	No

Supplementary Note 2

Overview of Tuned Machine Learning Hyperparameters

Classification algorithms:

Logistic Regression (LR):

- *penalty*: none, l2
- *C*: 0.001,0.01,0.1,1,10,100,1000

Gaussian process classifier (GPC):

- *kernel*: DotProduct, Matern, RationalQuadratic, WhiteKernel

Gaussian Naive Bayes (GNB):

- *var_smoothing*: 100 steps from -9 until +9

Random Forest Classifier (RFC):

- *n_estimators*: 100, 300, 700
- *max_depth*: 2,4,6
- *max_features*: 2,4,6

Regression algorithms:

Lasso regression:

- *selection*: “random”
- *alpha*: 1.0, 0.7, 0.5

Ridge regression

- *alpha*: 1.0, 0.7, 0.5

Elastic nets:

- *l1_ratio*=0.5
- *selection*="random"
- *alpha*: 1.0, 0.7, 0.5

Multi-layer perceptron regression:

- *activation*: "relu"
- *batch_size*: 64
- *early_stopping*: True
- *solver*: “adam”
- *alpha*: 1, 0.1, 0.01, 0.001, 0.0001

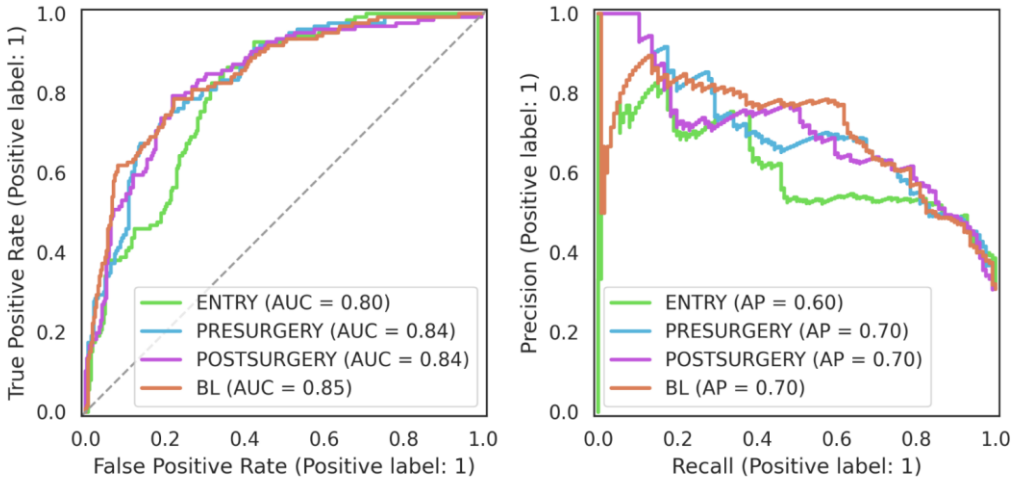
- *hidden_layer_size*: (10, 3), (11, 3), (8, 3), (7, 3), (9, 3)

Random Forest Regressor:

- *n_estimators*: 100, 300
- *max_depth*: 2,4
- *max_features*: 2,4

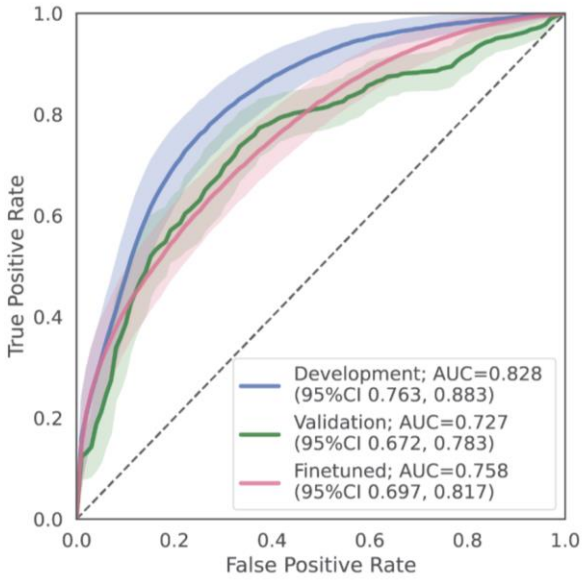
Supplementary Figure 1.

Comparison performance between different time-dependent datasets for the estimation of the presence of GAS. (left) ROC curve (right) Precision-Recall curve. ENTRY (upon hospital admission), PRESURGERY (prior to first surgical procedure), POSTSURGERY (posterior to first surgical procedure and prior to ICU admission), BL (baseline; first 24 h of ICU admission). AUC: Area under the ROC curve, AP: average precision.



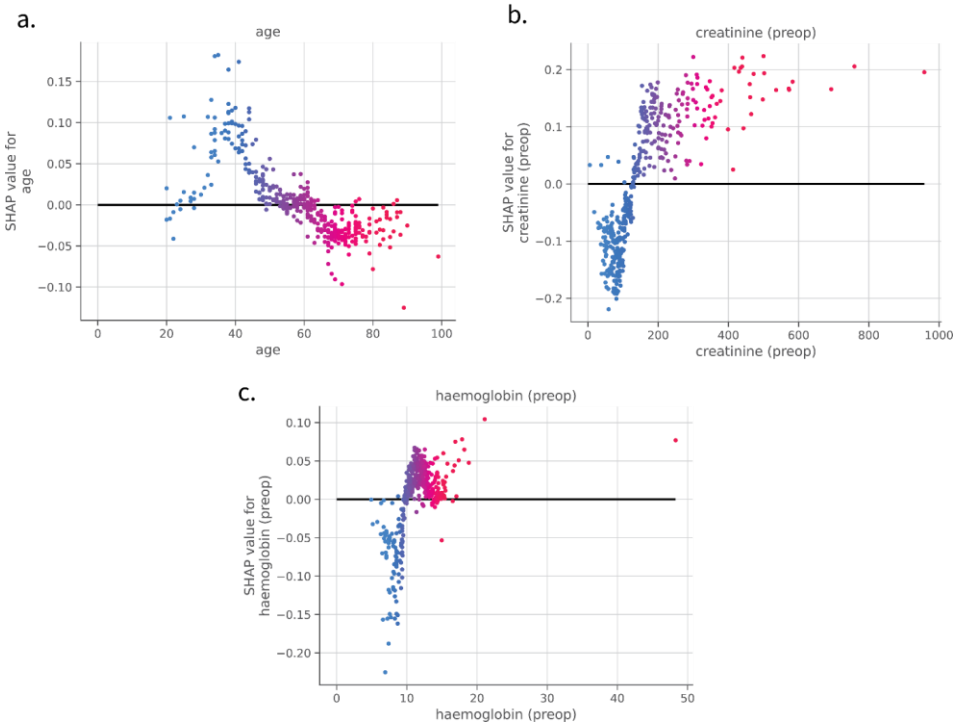
Supplementary Figure 2.

ROC-curves comparing the performance of the **development** (blue) and **external validation** (green), and **fine-tuned external validation** (pink). 95%CI: 95% confidence interval derived through 1000 (development) and 10000 (validation) bootstrapped samples



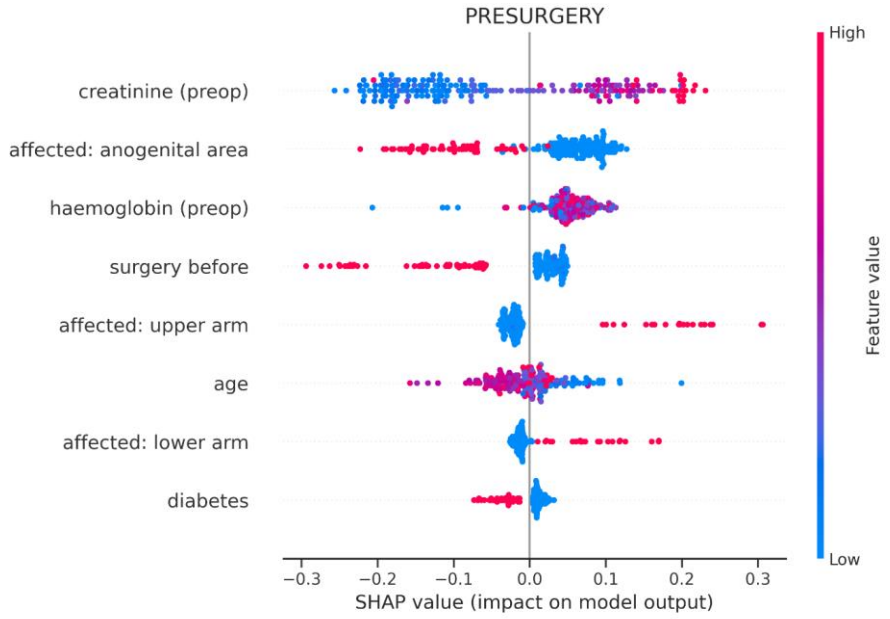
Supplementary Figure 3.

SHAP dependence plots for (a) age (b) creatinine (c) haemoglobin. The colour gradient denotes the variable values, with red indicating high values (e.g. age ~ 70 years) and blue indicating low values (e.g. age ~ 20 years).



Supplementary Figure 4.

SHAP values for models estimating the presence of GAS with the external validation cohort. Variables are sorted from most impactful (top, creatinine) to least impactful (bottom, diabetes), with every dot representing a patient. Positive SHAP values for a variable indicate a positive contribution to the model's decision to identify the patient as GAS-positive. Conversely, negative SHAP values indicate a contribution to classifying the patient as GAS-negative. The colour gradient denotes the variable values, with red indicating high values (e.g. age ~ 70 years) and blue indicating low values (e.g. age ~ 20 years).



Supplementary Table 1.

Overview of the number of patients included and data subsets assessed for each clinical outcome.

Outcome category	Outcome	No. of patients (n)	Time-dependent data subsets	Prediction task	No. of patients (%) or mean ± SD
causative microbes	Presence of GAS	409	Entry, pre-surgery, post-surgery, baseline	classification (y/n)	126 (30.8%)
surgical aspects	Risk of amputation	409	Entry, pre-surgery	classification (y/n)	54 (13.2%)
	Size of skin defect (after first surgery)	391	Entry, pre-surgery	regression (pct. of body surface)	4.9 ± 5.2
	Size of skin defect (maximal)	409	Post-surgery, baseline	regression (pct. of body surface)	6.4 ± 7.3
patient management	Length of ICU stay	402	Entry, pre-surgery, post-surgery, baseline	regression (days)	10.7 ± 10.8
organ support	Need for RRT (within 24h after ICU admission)	409	Entry, pre-surgery, post-surgery	classification (y/n)	57 (13.9%)
	Need for RRT (within 90 days)	351	Baseline	classification (y/n)	24 (6.8%)

Supplementary Table 2

Detailed description for variables used in the estimation of the presence of GAS.

Variable name	Description
age	age at admission [years]
affected: upper arm	affection of upper arm[1] [y/n]
affected: lower arm	affection of lower arm[1] [y/n]
affected: anogenital area	affection of anogenital area[1] [y/n]
surgery before	surgery within 4 weeks previous of NSTI [y/n]
diabetes	diabetes [y/n]
creatinine (preop)	Highest preoperative[2] creatinine [µmol/L]
haemoglobin (preop)	Lowest preoperative[2] haemoglobin [mmol/L]
creatinine (preadmission)	Highest preadmission[3] creatinine [µmol/L]
Lowest systolic BP (BL)	Lowest BL[4] systolic blood pressure [mmHg]
Creatinine (BL)	Highest BL[4] creatinine [µmol/L]
Noradrenaline (BL)	Highest noradrenaline infusion rate at BL[4] [µg/kg/min]
Platelets (BL)	Lowest BL[4] platelets [10^9/L]
Lactate (BL)	Highest BL[4] lactate level [mmol/L]
Glucose (BL)	Highest BL[4] glucose [mmol/L]
Anatomical site sampled	Anatomical site[5] specimen was sampled from

[1] at arrival at sepcialized hospital

[2] before the first surgery, which is before ICU admission

[3] upon ICU admission

[4] during the first 24 hours in the ICU

[5] one of the following: head/neck, u. arm, l. arm, hand, finger, thorax, abdomen, ano-gen., u. leg, l. leg, foot, to

Supplementary Table 3.

Overview of variables yielded through unsupervised variable selection for prediction of surgical, patient management, and organ support outcomes. BMI: Body Mass Index, BL: baseline (24 hours after ICu admission), CRP: c-reactive protein, preop: preoperative, KDIGO: Kidney Disease Improving Global Outcomes, WBC: white blood cell count,

Risk of amputation	**Size of skin defect (after first surgery)**	**Size of skin defect (maximal)**	**Days spent in ICU**	**Need for RRT (24h after ICU admission)**	**Need for RRT (90 days)**
Weight	Weight	BP (highest BL)	No. of blood samples taken	Weight	Pulse (lowest BL)
Height	Height	Bilirubin (highest BL)	Discoloration (preop)	Height	Carbamid (highest BL)
Discoloration (preop)	Bullae (preop)	No. of blood samples (1st surgery)	WBC (preop)	Discoloration (preop)	Potassium (highest BL)
Bruising (preop)	WBC (preop)	Blood collection mode	CRP (preop)	WBC (preop)	Bicarbonate (lowest BL)
WBC (preop)	CRP (preop)	Bullae (preop)	creatinine (preop)	CRP (preop)	Urine output (BL)
CRP (preop)	creatinine (preop)	WBC (preop)	Haemoglobin (preop)	creatinine (preop)	creatinine (preop)
creatinine (preop)	Natrium (preop)	Blood products (baseline)	Age	Natrium (preop)	creatinine (BL)
Natrium (preop)	Haemoglobin (preop)	Center code	affected: head/neck	Haemoglobin (preop)	Noradrenaline (max BL)
Haemoglobin (preop)	BMI	Bullae (during 1st surgery)	Varicella	BMI	pH (lowest BL)
BMI	Center code	Haemoglobin (preop)	Size of skin defect (after first surgery)	Age	SBE (lowest BL)
Age	Age	CRP (preop)		affected: upper leg	Lactate (highest BL)
	affected: abdomen			Cardiovascular disease present	Crystalloids (BL)
	affected: upper leg				Accumulated fluids (BL)
	affected: lower leg				KDIGO stage
					creatinine (preadmission)
					WBC (preop)
n = 11	**n = 14**	**n = 11**	**n = 10**	**n = 12**	**n = 16**

Supplementary Table 4.

Prediction performance for clinical endpoints revolving around surgical aspects, patient management, and organ support. Ave. prec.: average precision, R^2 coefficient of determination, MAE: mean absolute error, MSE: mean squared error

	Risk of amputation	Size of skin defect (after first surgery)	Size of skin defect (maximal)	Days spent in ICU	Need for RRT (24h after ICU admission)
Acc.	0.503 (0.483, 0.546)	-	-	-	0.543 (0.493, 0.610)
Prec.	0.137 (0.000, 1.000)	-	-	-	0.467 (0.000, 1.000)
Recall	0.020 (0.000, 0.106)	-	-	-	0.109 (0.000, 0.250)
F1-score	0.033 (0.000, 0.182)	-	-	-	0.168 (0.000, 0.345)
Brier	0.113 (0.092, 0.136)	-	-	-	0.105 (0.083, 0.125)
Ave. prec.	0.261 (0.159, 0.411)	-	-	-	0.385 (0.238, 0.540)
R^2	-	0.120 (0.044, 0.178)	0.179 (0.100,0.234)	0.018 (-0.063,0.056)	-
MAE	-	3.500 (3.144, 3.831)	4.383 (3.905, 4.879)	7.047 (6.194,7.976)	-
MSE	-	24.086 (16.334, 34.611)	43.328 (27.789, 66.054)	111.952 (65.077, 172.308)	-