Web-Based Application For Predicting Potential Target Phenotype For Recombinant Human Thrombomodulin Therapy In Patients With Sepsis: Analysis Of Three Multicentre Registries

Tadahiro Goto (tag695@mail.harvard.edu)
TXP Medical Co. Ltd
Daisuke Kudo
Tohoku University Graduate School of Medicine
Ryo Uchimido
Tokyo Medical and Dental University
Mineji Hayakawa
Hokkaido University Hospital
Kazuma Yamakawa
Osaka Medical and Pharmaceutical University
Toshikazu Abe
Tsukuba Memorial Hospital
Atsushi Shiraishi
Kameda Medical Center
Shigeki Kushimoto
Tohoku University Graduate School of Medicine

Short Report

Keywords: Recombinant human thrombomodulin, sepsis, phenotype, prediction model, coagulopathy

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1425804/v1

Abstract

A recent randomised controlled trial (RCT) failed to demonstrate a beneficial effect of recombinant human thrombomodulin (rhTM) on sepsis, but there is controversy in the effects of rhTM for sepsis due to heterogeneity of its study population. While we previously identified a distinct phenotype that could be a potential target of rhTM therapy, the discovery of phenotypes itself is insufficient because rules or prediction models are required to determine which patients are the potential target phenotypes of rhTM therapy in the clinical setting. Thus, using three multicentre sepsis registries, we aimed to develop and validate a machine learning model for predicting the target phenotype that we previously identified for targeted rhTM therapy. The predictors werer platelet counts, PT-INR, fibrinogen, fibrinogen/fibrin degradation products, and D-dimer. We also implemented the model as a web-based application. Two of the three registries were used for model development (n=3694), and the remaining registry was used for validation (n=1184). Approximately 9% of patients had the target phenotype in each cohort. In the validation, the C statistic of the developed model to predict the target phenotype was 0.996 (95% CI, 0.993-0.998), with a sensitivity of 0. 991and a specificity of 0. 967. Among patients those who were predicted as “potential target phenotype” in the validation cohort, rhTM use was associated with a lower in-hospital mortality (adjusted risk difference, −31.3% [−53.5% to −9.1%]). Given the high accuracy of the developed model for predicting the target phenotype for rhTM therapy, implementing the model as a web-based application could profoundly benefit clinicians and researchers conducting subsequent investigations to address heterogeneity in the treatment effects and its mechanisms.

Background

Recombinant human thrombomodulin (rhTM) has been suggested as an adjunct therapy for patients with sepsis [1]. A recent randomised controlled trial (RCT) failed to demonstrate its beneficial effect on 28-day mortality [2], but there remains controversy in the results of this study due to the heterogeneity of its study population. Indeed, 22% of patients in the RCT did not meet protocol-specified coagulopathy. In addition, an updated meta-analysis including the RCT reported an association between rhTM use and a lower risk of mortality [3]. These findings collectively suggest the importance of appropriately targeting the study population prior to conducting studies to gain maximum benefit [4–6]. To address this, we previously identified clinical phenotypes of sepsis in terms of coagulopathy using machine learning approaches [7]. We found a distinct phenotype that could be a potential target of rhTM therapy, a finding consistent with previously suggested target conditions, including “coagulation disorder” and “high disease severity” [8]. However, the discovery of phenotypes itself is insufficient for clinical use and designing subsequent studies because rules or prediction models are required to determine which patients are the potential target phenotypes in the clinical setting [9]. Thus, we aimed to develop and validate a prediction model for predicting the potential target phenotypes for rhTM therapy and to implement the model as a web-based application to facilitate further research.

Methods

Study design and settings

This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline for prognostic studies [10]. Details of this study are provided in **Supplemental Material**. This was a secondary analysis of the following multicentre registries: the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC-DIC) study (42 ICUs at 40 institutions, 2011–2013) [11], Tohoku Sepsis Registry (10 institutions, 2015) [12], and Focused Outcomes Research in Emergency Care for Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) sepsis study (59 ICUs, 2016–2017) [13]. These studies were approved by the institutional review boards at the participating hospitals and the need for informed consent was waived.

Study samples

We included all patients (aged ≥ 16 years), who were admitted to the ICUs with severe sepsis or septic shock as defined in the three registries, according to *the International Sepsis Definitions Conference criteria* [14, 15]. We excluded patients without information on 28-day mortality available, which is required for determining the phenotype of each patient [7].

Predictors

We used the following coagulation markers for predicting the presence of the target phenotype according to our previous study [7]: platelet counts, PT-INR, fibrinogen, fibrinogen/fibrin degradation products (FDP), and D-dimer.

Outcomes

The primary outcome was the presence of the clinical phenotype identified in our previous study [7]. The target phenotype was characterized as a severe physiological status and organ dysfunction (high acute physiology and chronic health evaluation [APACHE II] and sequential organ failure assessment [SOFA] scores), coagulopathy (low platelet count, prolonged PT-INR, low fibrinogen, and extremely high FDP and D-dimer levels), high lactate level, and high mortality.

Statistical analysis

We described patient characteristics and clinical course using summary statistics as appropriate.

We derived our prediction model using the JSEPTIC-DIC study and Tohoku Sepsis Registry (derivation cohort) and validated the model using the FORECAST sepsis study (validation cohort). We imputed missing predictors using the random forest method with the *missForest* package [16]. The characteristics of missing data were as reported in our previous study [7]. We did not calculate sample size in advance because we used all available data. The sample size for model development (n = 3694, of which 9% had the target phenotype) was enough to ensure precise predictions and minimise overfitting [17].

For model development, we divided the derivation cohort into the training set (70% of the full sample randomly chosen for model development and hyperparameter tuning) and test set (30% of the full

sample randomly chosen for internal validation). Using the training set, using the log-transformed predictors above, we constructed a prediction model with XGBoost. We used the grid search strategy to identify the best combination of hyperparameters using the *ranger* and *caret* packages with 10-fold cross validation.

We measured the prediction performance of the devloped model by computing 1) C statistics (i.e., the area under the receiver operating characteristic [ROC] curve) and 2) prospective prediction results.

In addition, among patients those who were predicted as “potential target phenotype”, we assessed the effect of rhTM on in-hospital and 28-day mortality using a generalised estimating equation to account for patient clustering within hospitals. The adjusted variables were selected according to the previous study [7] (see **Supplemental Material**). We also reported the number of patients who met the inclusion criteria for the SCARLET trial (cardiovascular and/or respiratory dysfunction, and PT-INR > 1.4 and a platelet count in the range from 30 to $150*10^9$/L) to illustrate the difference in the target study population between studies [2].

Lastly, we uploaded the model on a website (URL: http://research-kudo-prediction.s3-website-ap-northeast-1.amazonaws.com/). All analyses were performed with R statistical software version 3.6.1 (R Foundation for Statistical Computing).

Results

Patient characteristics were similar between the derivation and validation cohorts (Table 1). Likewise, characteristics of patients with the target phenotype were similar between cohorts. Approximately 9% of patients had the target phenotype. Among patients who met the inclusion criteria for the SCARLET trial, patients with the target phenotype accounted for 17% (96/577) and 23% (20/88) of the derivation cohort and validation cohort, respectively.

Table 1
Characteristics and clinical course of patients with sepsis in the derivation and validation cohorts.

	Derivation cohort		Validation cohort	
	Overall	Target phenotype	Overall	Target phenotype
Variables	n = 3694	n = 323	n = 1184	n = 108
Age, median (IQR)	72.0 (62.0, 81.0)	72.0 (58.0, 80.0)	73.0 (64.0, 81.0)	73.0 (64.0, 82.0)
Sex, female	1468 (39.7%)	164 (50.8%)	465 (39.3%)	45 (41.7%)
Body weight (kg), median (IQR)	54.7 (46.6, 64.2)	55.0 (47.5, 64.0)	55.0 (47.0, 65.0)	53.0 (46.5, 60.5)
Infection site				
Catheter-related	44 (1.4%)	1 (0.3%)	22 (1.9%)	6 (5.6%)
Bone/soft tissue	374 (11.7%)	20 (6.9%)	138 (11.7%)	7 (6.5%)
Cardiovascular	68 (2.1%)	13 (4.5%)	16 (1.4%)	5 (4.6%)
Central nervous system	63 (2.0%)	14 (4.8%)	23 (1.9%)	2 (1.9%)
Urinary tract	509 (15.9%)	71 (24.5%)	218 (18.4%)	31 (28.7%)
Lung/thoracic	827 (25.9%)	38 (13.1%)	367 (31.0%)	19 (17.6%)
Abdomen	1032 (32.3%)	94 (32.4%)	311 (26.3%)	25 (23.1%)
Other/unknown	278 (8.7%)	39 (13.4%)	89 (7.5%)	13 (20.1%)
APACHE II, median (IQR)	22.0 (17.0, 28.0)	26.0 (20.0, 33.0)	22.0 (16.5, 29.0)	27.0 (22.0, 32.0)
SIRS score, median (IQR)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	3.0 (2.3, 4.0)	3.0 (3.0, 4.0)
SOFA scores	9.0 (6.0, 12.0)	13.0 (10.0, 16.0)	8.4 (5.6, 11.0)	11.0 (9.0, 13.5)
Lab data				

Five coagulation markers (in bold) were used for prediction.

*Defined as patients with 1) coagulopathy (PT-INR > 1.4 and platelet count 30 to $150*10^9$/L) and 2) vasopressor use or mechanical ventilation use.

	Derivation cohort		Validation cohort	
White blood cell (10^3/μL), median (IQR)	11.3 (4.8, 17.8)	12.2 (4.6, 19.7)	11.3 (5.8, 17.7)	10.8 (6.3, 20.0)
Platelet (10^3/μL), median (IQR)	122.0 (65.0, 194.0)	59.5 (32.0, 92.0)	144.0 (90.0, 220.0)	68.0 (40.5, 120.5)
PT-INR, median (IQR)	1.3 (1.2, 1.6)	1.6 (1.4, 2.1)	1.2 (1.1, 1.4)	1.5 (1.3, 1.7)
Fibrinogen (mg/mL), median (IQR)	421.0 (296.0, 528.9)	231.0 (151.0, 311.0)	447.0 (327.5, 563.0)	276.8 (154.0, 381.0)
FDP (μg/mL), median (IQR)	17.6 (10.1, 36.2)	120.2 (79.2, 266.0)	21.8 (11.0, 46.7)	120.7 (93.0, 245.4)
D-dimer (μg/mL), median (IQR)	7.8 (3.9, 17.2)	51.9 (35.2, 113.0)	9.2 (4.3, 21.9)	60.1 (39.5, 105.6)
Antithrombin (%), median (IQR)	60.0 (50.8, 69.0)	52.0 (42.4, 60.5)	67.0 (55.0, 75.9)	55.0 (49.0, 65.6)
Lactate (mmol/L), median (IQR)	2.9 (1.7, 5.7)	5.3 (2.9, 10.1)	3.0 (1.8, 5.2)	4.6 (2.9, 7.3)
Patients who met the inclusion criteria for the SCARLET trial*				
Coagulopathy	633 (17%)	99 (31%)	162 (14%)	33 (31%)
Coagulopathy and respiratory/cardiovascular dysfunction	577 (16%)	96 (31%)	88 (8%)	20 (16%)
Management				
rhTM	969 (29.3%)	128 (44.1%)	242 (21.2%)	44 (44.4%)
Vasopressor use	2789 (75.5%)	289 (89.5%)	749 (63.3%)	77 (71.3%)
Renal replacement therapy	971 (26.3%)	135 (41.8%)	98 (8.3%)	16 (14.8%)
Steroids	894 (24.2%)	112 (34.7%)	345 (29.1%)	48 (44.4%)
Intravenous immunoglobulin	1088 (29.5%)	116 (35.9%)	94 (7.9%)	18 (16.7%)

Five coagulation markers (in bold) were used for prediction.

*Defined as patients with 1) coagulopathy (PT-INR > 1.4 and platelet count 30 to $150*10^9$/L) and 2) vasopressor use or mechanical ventilation use.

	Derivation cohort		Validation cohort	
Antithrombin	1092 (29.6%)	161 (49.8%)	131 (11.1%)	22 (20.4%)
Prognosis				
28-day death	753 (20.4%)	117 (36.2%)	216 (19.0%)	24 (24.5%)
In-hospital death	1186 (32.1%)	151 (46.8%)	269 (23.4%)	28 (28.0%)
Five coagulation markers (in bold) were used for prediction.				
*Defined as patients with 1) coagulopathy (PT-INR > 1.4 and platelet count 30 to 150*10^9/L) and 2) vasopressor use or mechanical ventilation use.				

Using the test set of the derivation cohort, we found that the C statistic of the developed model was 0.993 (95% CI, 0.989-0.997). Prospective prediction results were as follows: sensitivity 0.968, specificity 0.955, positive predictive value 0.669, and negative predictive value 0.997. **Figure 1** shows the prediction ability of the developed model in the validation cohort. Using the validation cohort, we found that the model had the high discrimination (C statistic, 0.996; 95% CI, 0.993-0.998). Prospective prediction results were as follows: sensitivity 0.991, specificity 0.967, positive predictive value 0.754, and negative predictive value 0.999.

Among patients those who were predicted as “potential target phenotype” in the validation cohort (n=130), with the limited sample size, rhTM use was associated with a lower in-hospital mortality (adjusted risk difference, −31.3% [−53.5% to −9.1%]; **Table 2**).

Table 2 Unadjusted and adjusted risk difference between recombinant thrombomodulin use and outcomes among patients those who were predicted as “potential target phenotype”

	In-hospital mortality		28-day mortality	
	Unadjsuted risk difference	Adjusted risk difference	Unadjsuted risk difference	Adjusted risk difference
Test set of the derivation cohort (n=118)	−22.0% (−40.6% to −3.4%)	−27.4% (−41.8% to −12.9%)	−20.0% (−38.2% to −1.8%)	−23.6% (−39.8% to −7.4%)
Validation cohort (108)	−15.1% (−31.1% to 1.0%)	−31.3% (−53.5% to −9.1%)	−8.4% (−24.7% to 8.0%)	−21.1% (−43.4% to 1.1%)

In the test set of derivation cohort, the adjusted variables were age, sex, comorbidities, and sequential organ failure assessment (SOFA) scores

In the validation cohort, the adjusted variables were age, sex, comorbidities, SOFA scores, and in-hospital management, including renal replacement therapy, and treatment with steroids, intravenous immunoglobulin, antithrombin, and vasopressors.

Discussion

We derived and validated a machine learning model that accurately predicts the target phenotype of rhTM in patients with sepsis. The prediction ability was C statistics of 0.994 in the validation cohort, with a sensitvity of 0.981 and a specificity of 0.944. Among patients those who were predicted as the “potential target phenotype” in the validation cohort, rhTM use was associated with a lower in-hospital mortality. In addition, we implemented the model as a web-based application for clinical and research use.

The importance of considering the heterogeneity in a study population and treatment effects has been emphasized in recent years [6]. As shown in the analysis of multiple sepsis registries and RCTs [5], clinical phenotypes were correlated with host-response patterns and clinical outcomes, and simulations suggested the presence of heterogeneity in treatment effects across phenotypes. Thus, such heterogeneity may at least partially explain the underlying mechanisms of failed RCTs in critical care [18, 19]. Indeed, most of the patients who met the inclusion criteria for the SCARLET trial in our study did not have the target phenotype (17%-23% in the target phenotype).

Subgroup analyses have been widely used to address treatment effect heterogeneity despite its limitations [20]. In particular, conventional subgroup analyses assess one characteristic at a time, which may not reflect biology or clinical practice where multiple factors are often synergistic [6]. To address this concern, several approches have been proposed: clustering algorithms to identify distinct clinical phenotypes, Bayesian hierarchical models, and adaptive enrichment [6]. Thus, we previously used clustering approaches, which is a sort of modern approach to address heterogeneity in the study population. While it is still challenging to find *true* phenotype, and we believe that our research process — 1) discovering the target phenotype, 2) implementing a model for predicting the phenotype, and 3) conducting studies for the optimal target population or exploring underlying mechanisms — is an efficient way of conducting future studies and advancing personalised medicine.

This study has several limitations. First, although we developed a prediction model to identify the target phenotypes of rhTM, it remains unclear whether the potential target is the *true* target of rhTM therapy. Second, the number of missing variables for prediction may have limited our findings, though we performed imputation using the random forest approach to overcome this. Finally, our data were derived from Japanese patients, and the generalisability of the results to other populations may be limited.

Conclusions

We developed a prediction model that accurately identified the optimal target phenotype of rhTM therapy. The implementation of the prediction model for the potential target phenotype as a web-based application could profoundly benefit clinicians and researchers conducting subsequent investigations to address heterogeneity in treatment effects and its mechanisms.

List Of Abbreviations

APACHE: Acute physiology and chronic health evaluation

FDP: Fibrinogen/fibrin degradation product

FORECAST: Focused Outcomes Research in Emergency Care for Acute Respiratory Distress Syndrome, Sepsis, and Trauma

ICU: Intensive care unit

JSEPTIC-DIC: Japan Septic Disseminated Intravascular Coagulation

PT-INR: Prothrombin time/international normalised ratio

RCT: Randomized controlled trial

rhTM: Recombinant human thrombomodulin

ROC: receiver operating characteristic

SOFA: Sequential organ failure assessment

Declarations

Ethics approval and consent to participate: The three original studies were approved and the need for informed consent was waived by the institutional review boards at the participating hospitals.

Consent for publication: Not applicable

Availability of data and materials: JSEPTIC-DIC data are publicly available (*Sci Data*. 2018;5:180243). Tohoku Sepsis Registry and FORECAST sepsis study are not publicly available because participants of this study did not agree that their data can be shared publicly.

Competing interests: D.K., M.H., and S.K. received personal fees from Asahi Kasei Pharma Corporation. T.G. is the Chief Scientific Officer at TXP Medical Co.Ltd.

Funding: None

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by DK, TG, RU, MH, TA, and AS. Statistical analyses were reviewed by RU, TA, and AS. The first draft of the manuscript was written by TG. The manuscript was reviewed and edited by DK, KY, TA, AS, and SK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript..

Acknowledgements: We thank Mr. Fujimori for implementing our prediction model as a web-based application and the core investigators of the FORECAST sepsis study (Appendix) for providing the dataset. We are grateful to all investigators involved in the JSEPTIC-DIC study, Tohoku Sepsis Registry, and the FORECAST sepsis study for contributing to the data collection and assessment.

References

1. Yamakawa K, Aihara M, Ogura H, Yuhara H, Hamasaki T, Shimazu T: **Recombinant human soluble thrombomodulin in severe sepsis: a systematic review and meta-analysis**. J Thromb Haemost 2015, **13**(4):508–519.
2. Vincent JL, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, Pettila V, Wittebole X, Meziani F, Mercier E *et al*: **Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy: The SCARLET Randomized Clinical Trial**. JAMA 2019, **321**(20):1993–2002.
3. Yamakawa K, Levy JH, Iba T: **Recombinant human soluble thrombomodulin in patients with sepsis-associated coagulopathy (SCARLET): an updated meta-analysis**. Crit Care 2019, **23**(1):302.
4. Angus DC, Chang CH: **Heterogeneity of Treatment Effect: Estimating How the Effects of Interventions Vary Across Individuals**. JAMA 2021, **326**(22):2312–2313.
5. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H *et al*: **Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis**. JAMA 2019, **321**(20):2003–2017.
6. Granholm A, Alhazzani W, Derde LPG, Angus DC, Zampieri FG, Hammond NE, Sweeney RM, Myatra SN, Azoulay E, Rowan K *et al*: **Randomised clinical trials in critical care: past, present and future**. Intensive Care Med 2022, **48**(2):164–178.
7. Kudo D, Goto T, Uchimido R, Hayakawa M, Yamakawa K, Abe T, Shiraishi A, Kushimoto S: **Coagulation phenotypes in sepsis and effects of recombinant human thrombomodulin: an analysis of three multicentre observational studies**. Crit Care 2021, **25**(1):114.
8. Yamakawa K, Umemura Y, Hayakawa M, Kudo D, Sanui M, Takahashi H, Yoshikawa Y, Hamasaki T, Fujimi S, Japan Septic Disseminated Intravascular Coagulation study g: **Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan**. Crit Care 2016, **20**(1):229.
9. Fujiogi M, Dumas O, Hasegawa K, Jartti T, Camargo CA: **Identifying and predicting severe bronchiolitis profiles at high risk for developing asthma: Analysis of three prospective cohorts**.

EClinicalMedicine 2022, **43**:101257.

10. Collins GS, Reitsma JB, Altman DG, Moons KG: **Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement**. Ann Intern Med 2015, **162**(1):55–63.
11. Hayakawa M, Yamakawa K, Saito S, Uchino S, Kudo D, Iizuka Y, Sanui M, Takimoto K, Mayumi T: **Nationwide registry of sepsis patients in Japan focused on disseminated intravascular coagulation 2011–2013**. Sci Data 2018, **5**:180243.
12. Kudo D, Kushimoto S, Miyagawa N, Sato T, Hasegawa M, Ito F, Yamanouchi S, Honda H, Andoh K, Furukawa H *et al*: **The impact of organ dysfunctions on mortality in patients with severe sepsis: A multicenter prospective observational study**. J Crit Care 2018, **45**:178–183.
13. Abe T, Ogura H, Shiraishi A, Kushimoto S, Saitoh D, Fujishima S, Mayumi T, Shiino Y, Nakada TA, Tarui T *et al*: **Characteristics, management, and in-hospital mortality among patients with severe sepsis in intensive care units in Japan: the FORECAST study**. Crit Care 2018, **22**(1):322.
14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R *et al*: **Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012**. Crit Care Med 2013, **41**(2):580–637.
15. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G *et al*: **2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference**. *Crit Care Med* 2003, **31**(4):1250–1256.
16. Stekhoven DJ, Buhlmann P: **MissForest–non-parametric missing value imputation for mixed-type data**. Bioinformatics 2012, **28**(1):112–118.
17. Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, Moons KGM, Collins G, van Smeden M: **Calculating the sample size required for developing a clinical prediction model**. BMJ 2020, **368**:m441.
18. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A *et al*: **Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial**. JAMA 2001, **286**(15):1869–1878.
19. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gardlund B, Marshall JC, Rhodes A, Artigas A *et al*: **Drotrecogin alfa (activated) in adults with septic shock**. N Engl J Med 2012, **366**(22):2055–2064.
20. Burke JF, Sussman JB, Kent DM, Hayward RA: **Three simple rules to ensure reasonably credible subgroup analyses**. BMJ 2015, **351**:h5651.

Figures

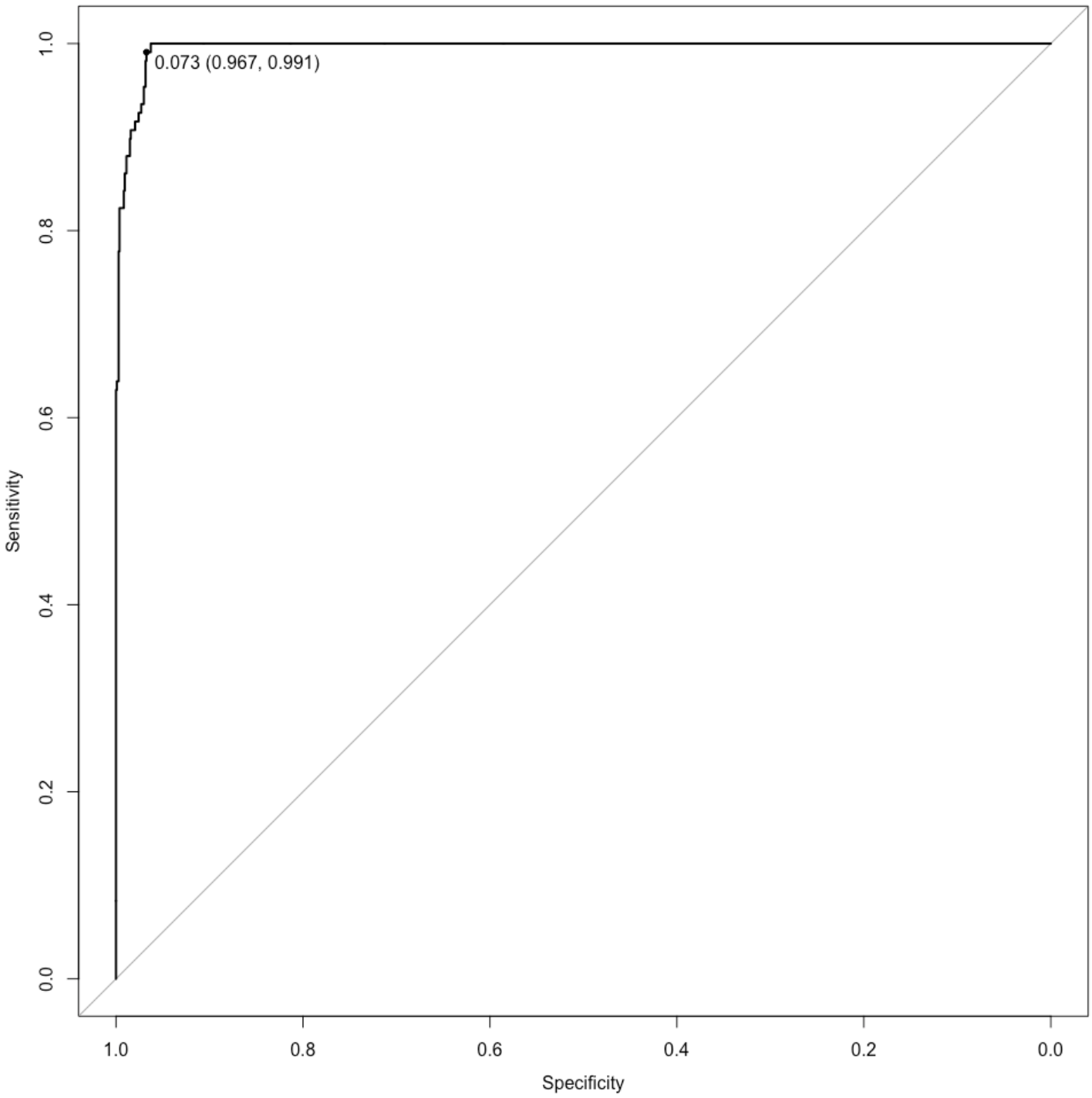

Figure 1

The receiver operating characteristic curve of the developed model for predicting the presence of the target phenotype in the external validation cohort

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Gotophenotypesepsispredictionspl.docx