

Development of a Mortality Prediction Model Combined With time to Positivity for Solid Tumor Patients with *Escherichia Coli* Bacteremia

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Abstract

Background: To develop a scoring model incorporating time to positivity (TTP) into clinical variables for predicting the mortality of tumor patients with *Escherichia coli* caused bloodstream infection (ECBSI).

Methods: A retrospective single center study enrolling hospitalized cancer patients with ECBSI was conducted from 2013 to 2018. The patients were randomly divided into development and validation groups. Univariable and multivariable logistic regression analysis were used to identify risk factors for mortality. The scoring model was developed and validated based on logistic regression coefficients.

Results: 315 and 194 patients with ECBSI were included in development and validation groups, respectively. Six significant risk factors for mortality were identified and included in the scoring model: fever $\geq 39^{\circ}\text{C}$, inappropriate antibiotic therapy, metastasis, acute respiratory distress (ARDS), blood transfusion, and TTP $\leq 8\text{h}$. Patients were classified into low-risk ($<10\%$ mortality), medium-risk ($10\%-20\%$ mortality) and high-risk ($\geq 20\%$ mortality) categories based on the predicted mortality rates in each score. The predicted mortality for the three categories was 4.38%, 15.39%, and 51.77%, respectively, in the development group, and 3.72%, 13.88%, and 50.09%, respectively, in the validation group. The model showed excellent discrimination and calibration for both groups, with AUC curves being 0.858 versus 0.835, respectively, and no significant difference in the Hosmer-Lemeshow test (6.709, $P=0.48$) and the Chi-square test (6.993, $P=0.46$). Sensitivity and negative predictive values (NPV) increased along with the decrease of cut-off values.

Conclusion: The developed TTP-combined scoring model is feasible for clinicians to predict the mortality risk of cancer patients with ECBSI.

Background

Escherichia coli (EC) is the most common cause of bloodstream infection (BSI) involving gram-negative bacteria. The incidence of EC-caused BSI (ECBSI) is increasing in the UK and Europe [1–3]. Also, EC was the predominant pathogen of BSI in the Asia-Pacific region (26.0% overall) [4]. In different regions of China, EC also ranked first in the top five bacteremia pathogens from 2011 to 2016 [5]. Multidrug resistance (*e.g.* ESBL) with EC has spread in recent decades and has become a major health problem worldwide. This problem is of particular concern among cancer patients with immunosuppressed status, who are at higher risk for severe sepsis and with poor outcome. Currently, treatment of ECBSI is still a challenge, which makes the morbidity and mortality in infected cancer patients high [6].

In order to estimate ECBSI-associated mortality, scoring models were established to predict the mortality risk in infected patients based on clinical and laboratory data. Al-Hasan et al developed a mortality prediction model for BSI patients by using the Pitt bacteremia score (PBS) together with other risk factors including malignancy, liver cirrhosis, and the non-urinary/CVC source of BSI [7]. This scoring model is applicable for gram-negative BSI patients who are properly treated with clinically acceptable empirical antimicrobial regimens. Yishu Tang et al. developed a prediction model that is suitable to identify

mortality risk factors for hematological malignant (HM) patients with BSI [8]. In addition, other studies about the mortality scoring system for BSI patients focused on critical patients, sepsis patients, and high-risk patients in the emergency department [9–12]. Because the variables of each study differed with the study object and the infected pathogen spectrum, these scoring models are not applicable to solid tumor patients with BSI. A previous study indicated that time to positivity (TTP) is a prognostic factor of the clinical outcome of bacteremia. TTP is a powerful predictor of mortality for certain organisms–caused bacteremia (*e.g. Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida species*) [13–16]. Therefore, we presumed that TTP might be a useful mortality predictor and could be incorporated into the risk-scoring model. This study aimed to develop a scoring model that combines TTP with clinical variables to predict in-hospital mortality in solid tumor patients.

Methods

Setting and study design

Patients were treated at Tianjin Medical University Cancer Institute and Hospital, which care for local and northern Chinese residents with cancer. All cases of solid tumor were confirmed by pathology. Cancer patients with ECBSI were identified based on their microbiology records, and enrolled between December 2013 and December 2018. Demographic and treatment information was extracted from their electronic medical records. Cancer patients with ECBSI were randomly assigned to development (two-thirds of the total number) and validation groups (one-third) by the grouping function of SPSS software. The development group was used to create the risk scoring model for in-hospital mortality. The performance of the scoring model was then assessed by the validation group. Only the first episode of BSI in the study period was included. Exclusion criteria for patients were: (1) polymicrobial bloodstream infections; (2) < 18 years old; (3) incomplete clinical data; (4) a recurrent BSI occurring in the same patient during the study period.

Microbiology analyses

Approximately 20 mL of blood from cancer patients was aseptically obtained via peripheral venipuncture, and equally distributed into BACTEC plus aerobic/F and anaerobic lytic/10 vials using the BACTEC FX400 Automated Blood Culture System (Becton Dickinson, Franklin Lakes, NJ, USA). This system monitors bacterial growth by measuring CO₂ production through a fluorescent sensor every 10 min for five days. Identification and susceptibility tests of strains were performed using the Vitek 2 automated system (bioMérieux, Marcy Etoile, France). The minimum inhibitory concentration (MIC) was interpreted using the Clinical and Laboratory Standards Institute (CLSI) breakpoints for all tested antibiotics [17].

ESBL-EC was further confirmed by performing a double-disc synergy test in accordance with CLSI guidelines [18]. *Escherichia coli* ATCC25922 (negative control) and *Klebsiella pneumoniae* ATCC 700603 (positive ESBL producer) (American Type Culture Collection, USA) were used for quality control.

Variables and definitions

The independent variables were available at the moment of the BSI, which included: age, gender, chronic morbidities, underlying tumor, ESBL, admission to ICU, metastasis, site of infection acquisition, acute respiratory distress syndrome (ARDS) at admission, presence of central line, TTP, neutropenia, and clinical treatments (such as blood transfusion and antibiotic therapy).

BSI was considered to be nosocomially acquired, health care related, or community acquired, applying criteria previously described [19]. Neutropenia was defined as an absolute neutrophil counts 500 neutrophils/ μL . We followed the Berlin criteria for ARDS [20]. Inappropriate antibiotic therapy was defined as the empiric administration of antimicrobial agents that were ineffective either in vivo or in vitro against the causative microorganism. In-hospital mortality was defined as death by any cause within the first 30 days after the onset of BSI during hospitalization.

Model setup and statistical analysis

The predictive score was calculated using the development group. Continuous variables of demographic and clinical data were reported as median and interquartile range (IQR). The Mann-Whitney U test was used to compare continuous variables, and the Chi-square test was used to compare categorical variables. Univariable and multivariable logistic regression analysis were used to determine the risk factors for the outcome of patients. Variables with a P value <0.05 in univariable logistic regression analysis in the development group, and those which were considered to be of clinical interest were included in a multivariable logistic regression model in order to identify significant risk factors for in-hospital mortality. Significant risk factors were assigned weighted points that were proportional to their β regression coefficient values. The risk scores were calculated for each individual patient in the group. Patients were categorized in deciles of risk score and then divided into three groups which were significantly distinct in predictive risk for mortality: low ($<10\%$ mortality), medium ($10\%-20\%$ mortality), and high risk ($>20\%$ mortality). Then, predictive mortality was calculated for each risk group. The discriminatory ability of the scoring model was evaluated by the area under a receiver operating characteristic (ROC) curve (AUC). AUC differences between the development and validation groups were compared using the Chi-square test. The positive predictive value (PPV), negative predictive value (NPV), predictive sensitivity, and predictive specificity of in-hospital mortality in the development group were calculated at different cutoff values. The scoring model was then applied to the validation group for confirmation. The best cut-off value was determined based on the Youden index statistics. All the analyses were performed using SPSS version 23 software (Chicago, IL, USA). A two-sided P value of <0.05 was considered statistically significant.

Results

Clinical characteristics of solid tumor patients with ECBSI

During the study period, clinical characteristics of 535 adult solid tumor patients with ECBSI were analyzed. Twenty-three recurrent episodes and three incomplete clinical data of ECBSI were excluded from the analysis. Thus, 509 solid tumor patients with a first episode of ECBSI were eligible for this study, and randomly assigned into the development group (315 patients) and validation group (194 patients). The clinical characteristics of development and validation groups are shown (Table 1). Overall, the median age was 61 years (interquartile range, IQR, 53–68 years). In-hospitalized mortality of overall patients was 22.2%. No significant differences were observed for all variables between the development and validation groups (Table 1), indicating that the grouping was random and the distribution of variables was even.

Table 1
Clinical characteristics of cancer patients with ECBSI

Variable	Validation (194)	Developmental (315)	P value
Gender			0.993
Male	98 (50.5%)	159 (50.5%)	
Female	96 (49.5%)	156 (49.5%)	
Age in years, median (IQR)	61 (53–68)	61 (53–68)	0.788
Fever $\geq 39^{\circ}\text{C}$	129 (66.5%)	199 (63.2%)	0.428
Co-morbidities			
Hypertension	55 (28.4%)	89 (28.3%)	0.984
Chronic heart disease	23 (11.9%)	41 (13.0%)	0.682
Diabetes mellitus	21 (10.8%)	39 (12.4%)	0.580
Underlying tumor			0.42
Lung tumor	14 (7.2%)	27 (8.6%)	
Hepatocellular tumor	38 (19.6%)	67 (21.3%)	
Gastroenterological tumor	34 (17.5%)	37 (11.7%)	
Mammary tumor	13 (6.7%)	18 (5.7%)	
Gynecological tumor	21 (10.8%)	35 (11.1%)	
Pancreatic tumor	33 (17.0%)	60 (19.0%)	
Colorectal tumor	15 (7.7%)	35 (11.1%)	
Genitourinary tumor	18 (9.3%)	16 (5.1%)	
Others ^a	8 (4.1%)	20 (6.3%)	
ESBL	105 (54.1%)	156 (49.5%)	0.313
ICU admission	14 (7.2%)	29 (9.2%)	0.433
Inappropriate antibiotic therapy, n (%)	47 (24.2%)	87 (27.6)	0.384
Metastasis	91 (46.9%)	163 (51.7%)	0.282
Site of infection acquisition, n (%)			0.107
Biliary infection	59 (30.4%)	99 (31.4%)	

^a Includes meningioma, 7; metastatic encephalon, 3; bone and soft tissue tumor, 13; thyroid neck tumor, 5.

Variable	Validation (194)	Developmental (315)	<i>P</i> value
Pulmonary infection	17 (8.8%)	44 (17%)	
Abdominal infection	60 (30.9%)	69 (21.9%)	
Urinary tract infection	26 (13.4%)	42 (13.3)	
Catheter-related	4 (2.1%)	13 (4.1%)	
Others	9 (4.6%)	24 (7.6%)	
Unknown origin	19 (9.8%)	24 (7.6%)	
ARDS at admission	8 (4.1%)	15 (4.8%)	0.729
Blood transfusion	57 (29.4%)	99 (31.4%)	0.604
Central line	82 (42.3%)	138 (43.8%)	0.688
TTP $\leq$ 8 h	42 (21.6%)	63 (20%)	0.655
Neutropenia	51 (26.3%)	24 (7.6%)	0.232
30-day mortality	40 (20.6%)	73 (23.2%)	0.5
^a Includes meningioma, 7; metastatic encephalon, 3; bone and soft tissue tumor, 13; thyroid neck tumor, 5.			

Development of the TTP-incorporated mortality-risk-scoring model

Clinical data of cancer patients with ECBSI in the development group were used to develop a risk-scoring model for predicting mortality. Univariable logistic regression analysis indicated that fever $\geq 39^{\circ}\text{C}$, inappropriate antibiotic therapy, metastasis, central line, blood transfusion, hypertension, ARDS and TTP ≤ 8 h were potential risk factors for in-hospital mortality (Table 2). Among these potential risk factors, fever $\geq 39^{\circ}\text{C}$ (OR = 2.93, 95% CI = 1.388–6.185, $p = 0.005$), inappropriate antibiotic therapy (OR = 3.636, 95% CI = 1.895–6.975, $p < 0.001$), metastasis (OR = 2.972, 95% CI = 1.443–6.119, $p = 0.003$), ARDS at admission (OR = 10.159, 95% CI = 2.678–38.529, $p = 0.001$), blood transfusion (OR = 2.884, 95% CI = 1.511–5.505, $p = 0.001$) and TTP ≤ 8 h (OR = 2.64, 95% CI = 1.28–5.444, $p = 0.009$) were significantly associated with in-hospital mortality in multivariable regression analysis, and were used to calculate the mortality risk score for tumor patients with ECBSI (Table 3). Weighted points were assigned to each of the final six risk factors using the linear transformation of the corresponding regression coefficient. A predictive risk score was calculated for each patient by adding all points associated with each risk factor (Table 3). The predicted mortality in each decile was examined to find the best cut-off points for consolidating patients into the three risk groups, which were significantly distinctive: low-risk group ($<$

10% mortality, 0–1 points), medium-risk group (10–20% mortality, 2 points), and high-risk group (> 20% mortality, > 2 points).

Table 2
Risk factors for mortality of cancer patients with ECBSI

Variable	Survived (242)	Died (73)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Gender			0.565		
Female	120 (49.6%)	39 (53.4%)			
Male	122 (50.4%)	34 (46.6%)			
Age in years, median (IQR)	62 (53.5– 68)	60 (52– 69.5)	0.925		
Fever $\geq 39^{\circ}\text{C}$	140(57.9%)	59(80.8%)	< 0.001	2.93(1.388–6.185)	0.005
ESBL	119(49.2%)	37(50.7%)	0.821		
ICU admission	20(8.3%)	9(12.3%)	0.292		
Co-morbidities					
Hypertension	75 (31.0%)	14 (19.2%)	0.045	0.66 (0.302– 1.445)	0.229
Chronic heart disease	31 (12.8%)	10 (13.7%)	0.862		
Diabetes mellitus	27 (11.2%)	12 (16.4%)	0.240		
Inappropriate antibiotic therapy, n (%)	48 (19.8%)	39 (53.4%)	< 0.001	3.636 (1.895– 6.975)	< 0.001
Metastasis	105 (43.4%)	58 (79.5%)	< 0.001	2.972(1.443– 6.119)	0.003
Site of infection acquisition, n (%)			0.368		
Biliary infection	79 (32.6%)	20 (27.4%)			
Pulmonary infection	37 (15.3%)	7 (9.6%)			
Abdominal infection	50 (20.7%)	19 (26%)			
Urinary tract infection	32 (13.2%)	10 (13.7%)			
Catheter-related	7 (2.9%)	6 (8.2%)			
Others	18 (7.4%)	6 (8.2%)			

Variable	Survived (242)	Died (73)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Unknown origin	19 (7.9%)	5 (6.8%)			
ARDS at admission	4 (1.7%)	11 (15.1%)	< 0.001	10.159 (2.678– 38.529)	0.001
Blood transfusion	63 (26.0%)	36 (49.3%)	< 0.001	2.884 (1.511– 5.505)	0.001
Central line	116 (47.9%)	22 (30.1%)	0.006	0.523 (0.257– 1.061)	0.072
TTP ≤ 8 h	38 (15.7%)	25 (34.2%)	0.001	2.64 (1.28–5.444)	0.009
Neutropenia	35 (14.5%)	16 (21.9%)	0.133		

Table 3
Independent risk factors for in-hospital mortality and risk score

Variable	β coefficient	OR (95% CI)	<i>P</i> value	Score points
TTP ≤ 8 h	1.025	2.788 (1.360–5.716)	0.005	1
Inappropriate antibiotic therapy	1.299	3.667 (1.921–7.000)	< 0.001	1
Metastasis	1.219	3.385 (1.67–6.861)	0.001	1
Fever ≥ 39°C	1.110	3.034 (1.448–6.357)	0.003	1
ARDS at admission	2.172	8.777 (2.337–3.296)	0.001	2
Blood transfusion	1.047	2.849 (1.499–5.414)	0.001	1

Note: The corresponding scores were assigned to construct the scoring points according to the partial regression coefficient of the variables. i.e., the corresponding β regression coefficient of each variable was divided by the minimum β regression coefficient (0.868) in the logistic regression analysis, then multiplied by the constant (2), and rounded to the nearest integer.

Validation of the TTP-incorporated mortality-risk-scoring model

The predicted mortality for low-risk, medium-risk, and high-risk categories was 4.38%, 15.39% and 51.77%, respectively in the development group, while those for the validation group were 3.72%, 13.88%, and 50.09%, respectively. No significant difference of predicted mortality was found between the development group and validation group (Fig. 1). The model had excellent discrimination both in development and in validation groups, with AUC curves being 0.858 (95% CI = 0.809–0.907) versus 0.835

(95% CI = 0.764–0.905), respectively (Fig. 2). The model also had good calibration both in development and in validation groups, with a non-significant difference in the Hosmer–Lemeshow test (6.709, $P=0.48$) and Chi-square test (6.993, $P=0.46$), respectively. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different thresholds are shown (Table 4). Cut-off scores of 1, 2, and 3 were determined based on the Youden index. In the development group, 93.1% sensitivity and 95.7% NPV were the result at a cut-off of 1. In contrast, 44.4% sensitivity and 66.7% PPV were the result at a cut-off of 3. Similarly, in the validation group, 92.5% sensitivity and 96.0% NPV were the results at a cut-off of 1, and 42.5% sensitivity and 73.9% PPV were the results at a cut-off of 3. On the other hand, high specificity (93.2%) and moderate PPV (66.7%) but high NPV (84.7%) were the results for the development group at a cut-off of 3. Similarly, 96.0% specificity and 73.9% PPV but 86.3% NPV were the results for validation group at a cut-off of 3. Obviously, sensitivity and NPV of the scoring model increased along with the decrease of cut-off values.

Table 4
Risk scoring performance for cancer patients with ECBSI

	Cut off	Sensitivity	Specificity	PPV	NPV
Validation group	3 points	42.5%	96.0%	73.9%	86.3%
	2 points	75.0%	82.1%	52.6%	92.5%
	1 point	92.5%	47.7%	31.9%	96.0%
Development group	3 points	44.4%	93.2%	66.7%	84.7%
	2 points	76.4%	80.2%	53.9%	91.8%
	1 point	93.1%	46.4%	34.5%	95.7%

Discussion

In the current study, we developed and validated a risk scoring model for predicting mortality of solid tumor patients with ECBSI. Unlike patients with hematologic malignancies [8, 21], ICU admission, ESBL, and neutropenia are not significant mortality-related risk factors for solid tumor patients in this study. We identified six predicted risk factors associated with mortality for solid tumor patients with EC-caused BSI. These variables are fever $\geq 39^{\circ}\text{C}$, inappropriate antibiotic therapy, metastasis, ARDS at admission, blood transfusion, and TTP ≤ 8 h. Based on these high-risk variables, a TTP-combined scoring model was developed to predict the BSI mortality. To our knowledge, this is the first scoring model associated with infected solid tumor patients. Only one study developed a TTP-incorporated scoring model for predicting vascular infections [22]. However, this TTP-incorporated scoring model aimed to stratify the mortality risk of adults with nontyphoid *Salmonella*–caused vascular infection (NTSVI). Because nontyphoid *Salmonella* bacteremia is not frequent, their scoring model is not applicable to BSI patients (especially cancer patients) caused by other bacteria.

Since the clinical characteristics and BSI features are unique in cancer patients, and a shorter TTP is associated with higher mortality in infected patients [23, 24], the TTP-combined scoring model could improve the capability in predicting in-hospital mortality for cancer patients with BSI. This point is well-demonstrated in development and validation groups, when our TTP-combined scoring model was applied. The prediction sensitivity is improved with the decrease of cut-off values. Although at a threshold of 3, the prediction sensitivity for both groups was relatively low (44.4% and 42.5%, respectively), high prediction specificity improves the targeting of patients with a higher mortality risk. Our scoring model showing that the predicted mortality increases along with increasing score (Fig. 1). This means that patients are likely to have a mild infection and a low mortality at a scale of 0 to 1. If the score increased, the patient could have a severe infection and a higher mortality. These indicate that it can be used as a screening tool to quickly identify high-risk patients who may benefit from early intervention. On the one hand, clinicians should pay more attention to tumor patients with fever, metastasis, or ARDS, and take appropriate treatment measures as early as possible. On the other hand, inappropriate antibiotic therapy is associated with mortality in patients with BSI. Lack of early drug sensitivity may be a cause. Therefore, once the laboratory knows the result of susceptibility, it can provide advice on effective drugs in time. Moreover, we found that the *in vitro* susceptibility tests results were sensitive, but the antibiotics application on tumor patients was frequently ineffective. This implies there may have certain pathophysiological variables in cancer patients, especially in advanced patients, which impair the antibacterial effect and increase the renal clearance rate. Therefore, it is necessary to consider the optimal dosing and tailored individual regimens of antimicrobials in clinical medication. ARDS is more often fatal in patients with malignancy. In this study, the mortality of tumor patients with ARDS was accounted for 69% (16/23). Previously study showed that the mortality of cancer patients with ARDS was worse (54%) than those without cancer (24%). There are several potential explanations that cancer patients are prone to unique conditions that lead to acute respiratory failure, including severe infectious conditions such as resistant bacterial, fungal, and viral infections. In addition, they may have severe acute lung injury related to chemotherapeutic agents and radiation [20]. Given the high mortality associated with ARDS in cancer patients, efforts should be taken to prevent acute lung injury in cancer patients. It was suggested that early utilization of chest computed tomography scan with high-resolution, serological tests such as galactomannan and Cytomegalovirus (CMV) antigen, and bronchoscopy with bronchodilator lavage (BAL) could improve the diagnostic yield and outcome of cancer patients with acute respiratory problems.

Of note, blood transfusion as a predictor of BSI in solid tumor patients has rarely been noticed. Anemia is frequently observed in advanced tumor patients, either due to chronic illness or active bleeding. Blood transfusion supplements blood volume and improves microcirculation, and the increased plasma protein promotes coagulation. However, several studies showing that transfusion of some blood components (RBC, Platelet, fresh plasma and cryoprecipitate) may actually lead to negative clinical outcomes in cancer patients [20]. This may be due to a decreased immune surveillance, as a consequence of the transfusion of residual viable leucocytes, apoptosis cells, and various biological response modifiers (BRMs) present in packed RBCs [25]. Thus, blood transfusion should be regarded as a personalized

medicine, taking into careful consideration the status and specificity of tumor patient in order to reduce the negative effects.

Obviously, this study still had some limitations. First, since the study was performed at a single center in China, HCC comprises the most common solid tumor, followed by pancreatic cancer. HCC is less common in the North America and Europe. The difference in expected cancer type would impact the predictive power of this model outside of China. Second, no uniform standard is available for variables in the prediction model and it needs further validation by multiple center research in the future.

Conclusion

In a summary, we developed a risk scoring model that combines TTP with other clinical variables to predict in-hospital mortality for solid tumor patients with ECBSI. Our scoring model shows excellent discrimination for mortality prediction. This TTP-combined scoring model is feasible for clinicians to predict the mortality of ECBSI cancer patients, and is of benefit for accurate diagnosis and evidence-based therapeutic choice.

Abbreviations

TTP

time to positivity; EC:Escherichia coli; BSI:bloodstream infection; ECBSI:Escherichia coli caused bloodstream infection; ARDS:acute respiratory distress; IQR:interquartile range; ROC:receiver operating characteristic; AUC:area under a ROC curve; PPV:positive predictive value; NPV:negative predictive values; PBS:Pitt bacteremia score; HM:hematological malignant; MIC:minimum inhibitory concentration; CLSI:Clinical and Laboratory Standards Institute

Declarations

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Authors' contributions

All authors contributed to data analysis, drafting, or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital, waiving of informed consent was obtained due to the retrospective non-interventional study design.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

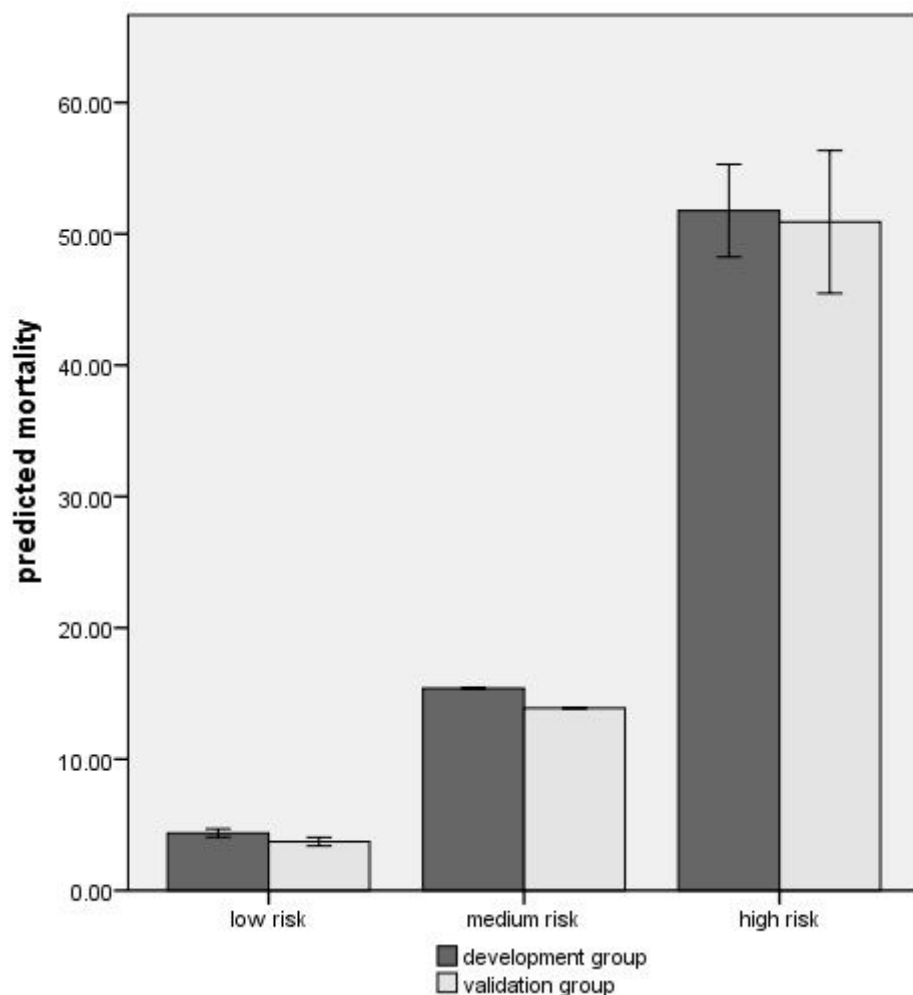


Figure 1

Predicted mortality by the TTP-combined scoring model

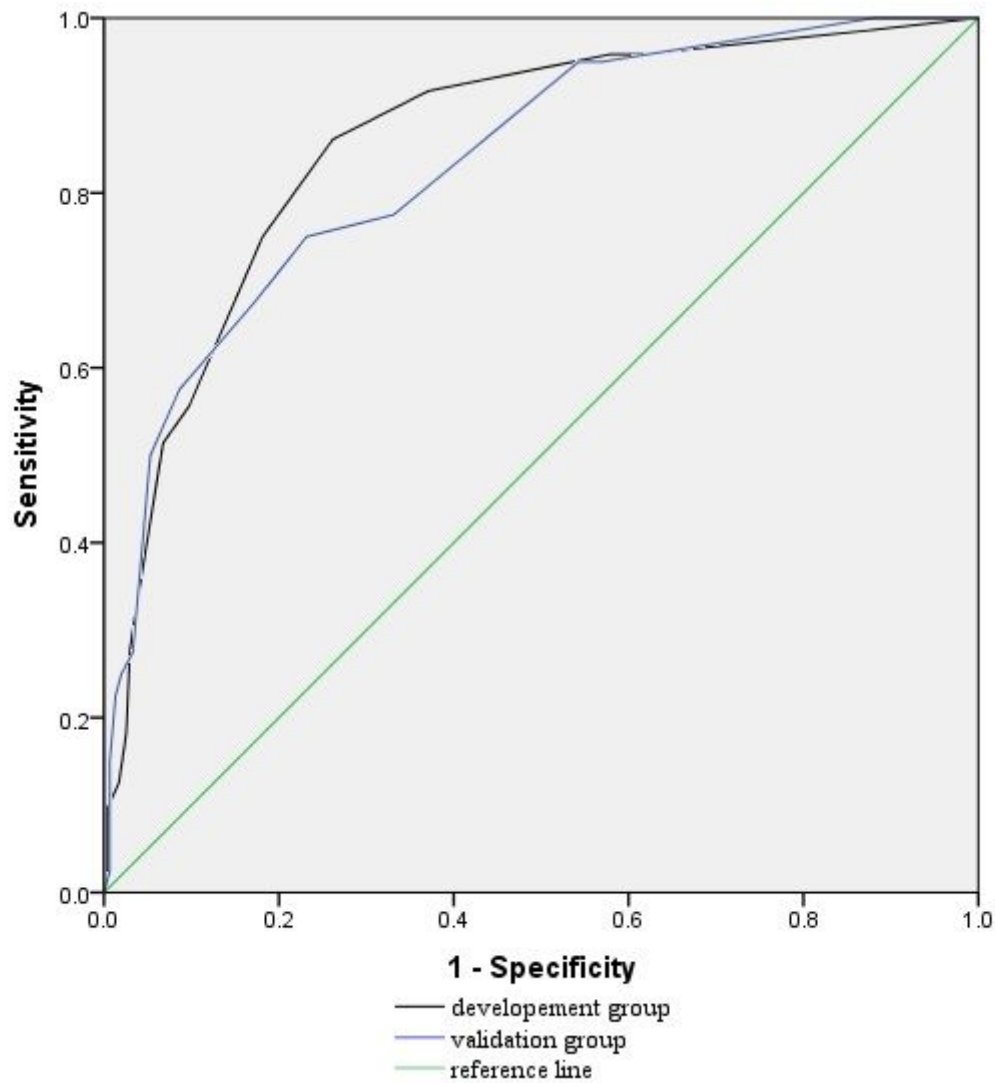


Figure 2

ROC curves of the TTP-combined scoring model