

Age, Pulse, Urea and Albumin (APUA) Model: A Tool for Predicting in-Hospital Mortality of Community-Acquired Pneumonia Adapted for Patients with Type 2 Diabetes

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Objective: The aim of this study was to develop a tool for predicting in-hospital mortality of community-acquired pneumonia (CAP) in patients with type 2 diabetes (T2DM).

Methods: A retrospective study was conducted on 531 CAP patients with T2DM at The First Hospital of Qinhuangdao. The primary outcome was in-hospital mortality. Variables to develop the nomogram were selected using multiple logistic regression analysis. Discrimination was evaluated using receiver operating characteristic (ROC) curve. Calibration was evaluated using the Hosmer–Lemeshow test and calibration plot.

Results: Multiple logistic regression analysis showed that age, pulse, urea and albumin (APUA) were independent risk predictors. Based on these results, we developed a nomogram (APUA model) for predicting in-hospital mortality of CAP in T2DM patients. In the training set, the area under the curve (AUC) of the APUA model was 0.814 (95% CI: 0.770–0.853), which was higher than the AUCs of albumin alone, CURB-65 and Pneumonia Severity Index (PSI) class ($p < 0.05$). The Hosmer–Lemeshow test ($\chi^2 = 5.298$, $p = 0.808$) and calibration plot ($p = 0.802$) showed excellent agreement between the predicted possibility and the actual observation in the APUA model. The results of the validation set were similar to those of the training set.

Conclusion: The APUA model is a simple and accurate tool for predicting in-hospital mortality of CAP, adapted for patients with T2DM. The predictive performance of the APUA model was better than CURB-65 and PSI class.

Keywords: community-acquired pneumonia, albumin, mortality, type 2 diabetes

Plain Language Summary

Current Knowledge

Community-acquired pneumonia (CAP) is more common in patients with diabetes, especially type 2 diabetes (T2DM). CURB-65 and pneumonia severity index (PSI) are two classical tools for evaluating the severity of CAP. However, the predictive performances of CURB-65 and PSI class were poor in patients with diabetes. Albumin is a protein made by the liver that plays many important roles. Low serum albumin was associated with the risk of mortality in T2DM patients with infection.

What This Paper Contributes to the Existing Knowledge

In this study, age, pulse, urea and albumin (APUA) model were independent risk predictors for in-hospital mortality of CAP in T2DM patients. Based on these

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results, we developed a nomogram (APUA model) for predicting in-hospital mortality of CAP in T2DM patients. The APUA model is a simple and accurate tool for predicting in-hospital mortality of CAP, adapted for patients with T2DM. The predictive performance of the APUA model was better than CURB-65 and PSI class.

Introduction

Community-acquired pneumonia (CAP) is a common respiratory disease, with an incidence of 1.76–9.6 per 1000 person-years.^{1–5} Diabetes is another global problem. About 463 million adults were living with diabetes worldwide in 2019.⁶ Patients with diabetes have an increased risk of up to 1.4 for CAP.⁷ Type 2 diabetes (T2DM) is the most common type. Therefore, CAP is more common in patients with diabetes, especially T2DM.

The outcomes varied enormously between different CAP patients, from rapid recovery to death. CURB-65 and Pneumonia Severity Index (PSI) are two classical tools for evaluating the severity of CAP and are recommended by several CAP guidelines.^{8–11} A previous meta-analysis showed that the area under the curves (AUCs) of CURB-65 and PSI were about 0.8 for predicting 30-day mortality in hospitalized CAP patients.¹² However, the predictive performances of CURB-65 and PSI class were poor in patients with diabetes. The AUCs of CURB-65 and PSI were only 0.669 and 0.682 in patients with T2DM.¹³

Albumin is a protein made by the liver that plays many important roles. Numerous studies confirmed that serum albumin correlated with short-term and long-term mortality of CAP.^{14–17} In the CAP-China network, albumin level was also an independent predictor of 60-day mortality of CAP.¹⁸

Serum albumin is closely related to the risk of death in T2DM. The level of albumin was negatively correlated with early mortality among elderly patients with T2DM.¹⁹ Low albumin levels increase the risk of mortality in diabetic patients with diabetic foot and chronic kidney disease.^{20,21} Low serum albumin was also associated with the risk of mortality in T2DM patients with infection. In T2DM, low albumin levels increase the risk of mortality in patients with community-onset bacterial bloodstream infections.^{22,23}

Therefore, in this study, we developed a tool for predicting in-hospital mortality of CAP in patients with T2DM.

Methods

Subjects

The patients in this study were included from a survey on in-hospital mortality of CAP in patients with T2DM at our hospital. All subjects were adult inpatients, who were hospitalized due to CAP between January 2015 and December 2018. Patients with type 1 diabetes, other specific types of diabetes, no clear type classification, pre-diabetes, pregnancy and obstetric infection were excluded. Patients with missing clinical data on serum albumin, CURB-65 and PSI were also excluded. Eventually, 2365 patients, aged 66.6±17.3 years, were enrolled. Among these patients, 531 were T2DM patients (22.5%), while 1834 were non-diabetics. This study was approved by the ethics committee of the First Hospital of Qinhuangdao.

Data Collection

Initial data after admission were extracted from the Hospital Information System. Sociodemographic variables included age, gender and ethnicity. Serum albumin, CURB-65 and PSI were also collected. The scores of CURB-65 and PSI were calculated.^{24,25} According to the PSI score, the patients were classified into five risk classes. The primary outcome was in-hospital mortality.

Statistical Analyses

The statistical analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL), R version 3.6.1 (R Development Core Team; <http://www.r-project.org>) and MedCalc15.2.2 (Ostend, Belgium) software. A *p*-value <0.05 was considered statistically significant.

For nomogram development and validation, we randomly assigned 70% of the participants to the training set and 30% to the validation set. The characteristics of the two sets were described and compared using chi-square test or Student's *t*-test. Variables to develop the nomogram were selected using multiple logistic regression analysis.

Nomogram validation consisted of two parts, discrimination and calibration. Discrimination was evaluated using receiver operating characteristic (ROC) curve, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Calibration was evaluated using the Hosmer–Lemeshow test and calibration plot. Clinical

Table 1 Characteristics of the Training and Validation Set in Community-Acquired Pneumonia Patients with Type 2 Diabetes

Variables		All (N=531)	Training Set (N=359)	Validation Set (N=172)	t or χ^2	P
Sex (males/females)		305/226	212/147	93/79	1.181	0.277
Age (years)		71.7±11.7	72.0±11.6	71.1±11.9	0.826	0.409
Ethnicity [n(%)]	Han	509(95.9)	342(95.3)	167(97.1)	2.879	0.237
	Other	15(2.8)	13(3.6)	2(1.2)		
	Unknown	7(1.3)	4(1.1)	3(1.7)		
Confusion [n(%)]		63(11.9)	43(12.0)	20(11.6)	0.014	0.907
Temperature (°C)		36.9±0.8	36.9±0.8	36.9±0.8	0.390	0.697
Respiratory rate (/min)		21.1±3.7	21.2±3.8	20.8±3.4	0.899	0.369
Pulse (/min)		89.7±18.2	90.7±18.5	87.6±17.4	1.851	0.065
SBP (mmHg)		135.8±24.7	134.9±24.3	137.6±25.5	1.168	0.243
DBP (mmHg)		77.5±13.8	77.0±12.7	78.4±15.9	1.103	0.271
Urea (mmol/L)		8.19±5.85	8.20±5.79	8.16±5.98	0.075	0.940
Sodium (mmol/L)		137.1±6.6	137.1±6.7	137.1±6.3	0.081	0.935
Glucose (mmol/L)		10.8±5.0	10.9±5.2	10.5±4.5	0.815	0.415
Hematocrit (%)		35.9±6.7	36.1±6.7	35.5±6.7	1.002	0.317
Albumin (g/L)		34.2±5.2	34.5±5.1	33.7±5.5	1.683	0.093
CURB-65 Score		1.42±0.99	1.44±0.98	1.37±1.01	0.744	0.457
PSI Score		96.5±29.5	96.9±29.5	95.5±29.6	0.524	0.600
Death [n(%)]		47(8.9)	34(9.5)	13(7.6)	0.527	0.468

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PSI, Pneumonia Severity Index.

effectiveness was evaluated using the decision curve analysis (DCA).

Results

This study enrolled 531 CAP patients with T2DM (305 males and 226 females), aged 71.7±11.7 years. The participants were randomly divided into the training set (n=359) and the validation set (n=172). No statistically significant differences in baseline characteristics, CURB-65, PSI and in-hospital mortality were observed between the two sets (Table 1).

In the univariate analyses, the frequencies of age ≥85 yrs, respiratory rate ≥30/min, pulse ≥125/min, urea ≥11 mmol/L, albumin 25–34.9 g/L and albumin ≥35 g/L were significantly higher in the dead patients than in the surviving patients ($p<0.05$) (Table 2). Multivariate analyses were performed using the significant risk factors determined in the univariate analysis. Multiple logistic regression analysis showed that age, pulse, urea and albumin (APUA) were independent risk predictors (Table 3).

Based on these results, we developed a nomogram (APUA model) for predicting in-hospital mortality of CAP in T2DM patients. The nomogram illustrated that serum albumin had the largest contribution to prognosis

in the APUA model (Figure 1). For example, a patient aged 87 years (62.02 points) had pulse 94/min (0 point), urea 7.3 mmol/L (0 point) and albumin 30.6g/L (63.23 points). The total score was 62.02 +0 + 0 + 63.23 = 125.25, and the predicted risk of in-hospital mortality was 17.6%. A web calculator based on the APUA model was developed to estimate the individualized risk of in-hospital mortality (<https://doctorma.shinyapps.io/DynNomapp/>).

In the training set, the AUC of the APUA model was 0.814 (95% CI: 0.770–0.853), which was higher than the AUCs of albumin alone, CURB-65 and PSI class ($p<0.05$) (Table 4) (Figure 2A). Compared with albumin alone, CURB-65 and PSI class, the NRIs of the APUA model were 0.861 (0.533–1.189), 0.766 (0.462–1.070) and 0.815 (0.493–1.137), respectively ($p<0.001$) (Table 5). The IDIs of the APUA model were 0.080 (0.032–0.127), 0.087 (0.040–0.134) and 0.076 (0.023–0.128), respectively ($p<0.05$) (Table 5). The Hosmer–Lemeshow test ($\chi^2=5.298$, $p=0.808$) and calibration plot ($p=0.802$) showed excellent agreement between the predicted possibility and the actual observation in the APUA model (Figure 3A). In the DCA, the APUA model showed better net benefit than albumin alone, CURB-65 and PSI class (Figure 4A).

Table 2 Characteristics of the Survival and Death Patients in the Training Set

Variables	Survival (N=325)	Death (N=34)	t or χ^2	P
Sex (males/females)	193/132	19/15	0.156	0.693
Age (years)	71.5±11.5	76.7±10.9	2.497	0.013
Age<64yrs	89(27.4)	4(11.8)	7.433	0.024
Age 65~84yrs	196(60.3)	21(61.8)		
Age ≥85yrs	40(12.3)	9(26.5)		
Ethnicity [n(%)]				
Han	310(95.4)	32(94.1)	0.954	0.621
Other	11(3.4)	2(5.9)		
Unknown	4(1.2)	0(0.0)		
Confusion [n(%)]	36(11.1)	7(20.6)	1.816	0.178
Temperature (°C)	36.9±0.8	36.9±1.0	0.312	0.755
Temperature <35°C or ≥40°C [n(%)]	0(0.0)	0(0.0)		
Respiratory rate (/min)	21.0±3.6	22.7±5.7	1.667	0.104
Respiratory rate ≥30/min [n(%)]	14(4.3)	5(14.7)	4.727	0.030
Pulse (/min)	89.2±17.1	105.4±24.8	3.711	0.001
Pulse≥125/min [n(%)]	12(3.7)	6(17.6)	9.826	0.002
SBP (mmHg)	135.2±23.6	132.1±30.0	0.579	0.566
DBP (mmHg)	77.0±12.6	76.6±13.4	0.193	0.847
SBP <90mmHg [n(%)]	6(1.8)	2(5.9)		0.170*
Low BP(SBP<90 or DBP≤60mmHg) [n(%)]	35(10.8)	4(11.8)	0.000	1.000
Urea (mmol/L)	7.87±5.51	11.32±7.37	3.350	0.001
Urea≥11mmol/L [n(%)]	53(16.3)	16(47.1)	18.747	<0.001
Sodium (mmol/L)	137.4±6.6	134.4±7.9	2.508	0.013
Sodium<130mmol/L [n(%)]	31(9.5)	6(17.6)	1.400	0.237
Glucose (mmol/L)	10.78±5.06	12.14±6.66	1.443	0.150
Glucose≥14mmol/L [n(%)]	61(18.8)	8(23.5)	0.449	0.503
Hematocrit (%)	36.4±6.8	34.0±5.9	1.945	0.053
Hematocrit<30% [n(%)]	56(17.2)	6(17.6)	0.004	0.951
Albumin (g/L)	34.8±5.0	31.7±4.7	3.465	0.001
Albumin <25g/L	165(50.8)	5(14.7)	20.840	<0.001
Albumin 25~34.9 g/L	155(47.7)	26(76.5)		
Albumin≥35 g/L	5(1.5)	3(8.8)		

Note: *Fisher's exact test.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

In the validation set, the AUC of the APUA model was 0.796 (0.728–0.854), which was higher than the AUCs of albumin alone, CURB-65 and PSI class, although without statistically significant differences ($p>0.05$) (Table 4) (Figure 2B). Compared with albumin alone, CURB-65 and PSI class, the NRIs of the APUA model were 0.599 (0.041–1.157), 0.693 (0.170–1.216) and 0.643 (0.119–1.166), respectively ($p<0.05$) (Table 5). Compared with albumin alone, CURB-65 and PSI class, the IDIs of the APUA model were 0.109 (0.027–0.191) and 0.086 (0.005–0.168), respectively ($p<0.05$) (Table 5). The Hosmer–Lemeshow test ($\chi^2=7.426$, $p=0.593$) and

calibration plot ($p=0.181$) showed excellent agreement between the predicted possibility and the actual observation in the APUA model (Figure 3B). In the DCA, the APUA model showed better net benefit than albumin alone, CURB-65 and PSI class (Figure 4B).

The sensitivities, specificities and Youden's index are shown in Table 6. The optimal cutoff point of the APUA model was the predicted risk of in-hospital mortality $\geq 10\%$. The sensitivity was 68.1% and the specificity was 80.2%. The patients were divided into five groups according to the predicted risk of mortality by the APUA model. The actual mortalities increased

Table 3 The Risk Factors of in-Hospital Mortality in the Training Set

Variables		OR	95% CI	P
Aging	Age<64yrs	1		
	Age 65~84yrs	2.224	0.691~7.159	0.180
	Age≥85yrs	4.780	1.299~17.591	0.019
Pulse≥125/min Urea≥11mmol/L		3.782	1.139~12.558	0.030
		3.510	1.583~7.784	0.002
Hypoproteinemia	Albumin≥35 g/L	1		
	Albumin 25~34.9 g/L	4.929	1.787~13.595	0.002
	Albumin<25g/L	12.463	1.933~80.353	0.008

Notes: Multiple logistic regression analysis, in-hospital mortality was considered as the dependent variables in a multiple logistic regression analysis with aging, respiratory rate≥30/min, pulse≥125/min, urea≥11mmol/L and hypoproteinemia as independent variables.

Abbreviations: OR, odds ratio; CI, confidence interval.

with the predicted risk of mortality by the APUA model (Table 7).

Discussion

This study established a tool termed the APUA model for predicting mortality of CAP, adapted for patients with T2DM. The APUA model is based on serum albumin, and consists of age, pulse, urea and albumin. This model has several advantages. First, the APUA model is relatively simpler and consists of only four risk factors. Urea and albumin can be tested in both primary and tertiary hospitals. Hence, the APUA model can be used in many medical institutions. Second, the APUA model

is a fast assessment system. These factors can be rapidly obtained after admission, and the severity of CAP can be quickly evaluated by the APUA model. Moreover, a web calculator was developed, which is convenient for use in clinical application. Third, the APUA model is suitable for T2DM patients with CAP. In T2DM patients with CAP, simple APUA model was superior to CURB-65 and PSI class. The AUCs of the APUA model were about 0.8 for predicting in-hospital mortality of CAP, and were higher than CURB-65 and PSI class. NRI and IDI are two novel metrics for evaluating improvement in discrimination. AUC, NRI and IDI offer complementary information. In this study, the results of NRI and IDI were in accordance with the results of AUC. DCA was performed to assess the performance of the APUA model. The net benefit of the APUA model was better than CURB-65 and PSI class.

Studies from Japan and Korea showed that serum albumin is not less accurate than CURB-65 or PSI class for predicting 30-day mortality in CAP patients.^{26,27} In this study, hypoalbuminemia was closely correlated with in-hospital mortality of CAP in T2DM patients. Compared to T2DM patients with albumin ≥35 g/L, T2DM patients with albumin 25–34.9 g/L [OR= 4.929] and albumin <25 g/L [OR= 12.463] were more likely to die at the time of hospitalization. The predictive accuracy of albumin alone was similar to CURB-65 or PSI class, which may be related to the following mechanisms. First, hypoalbuminemia was common in

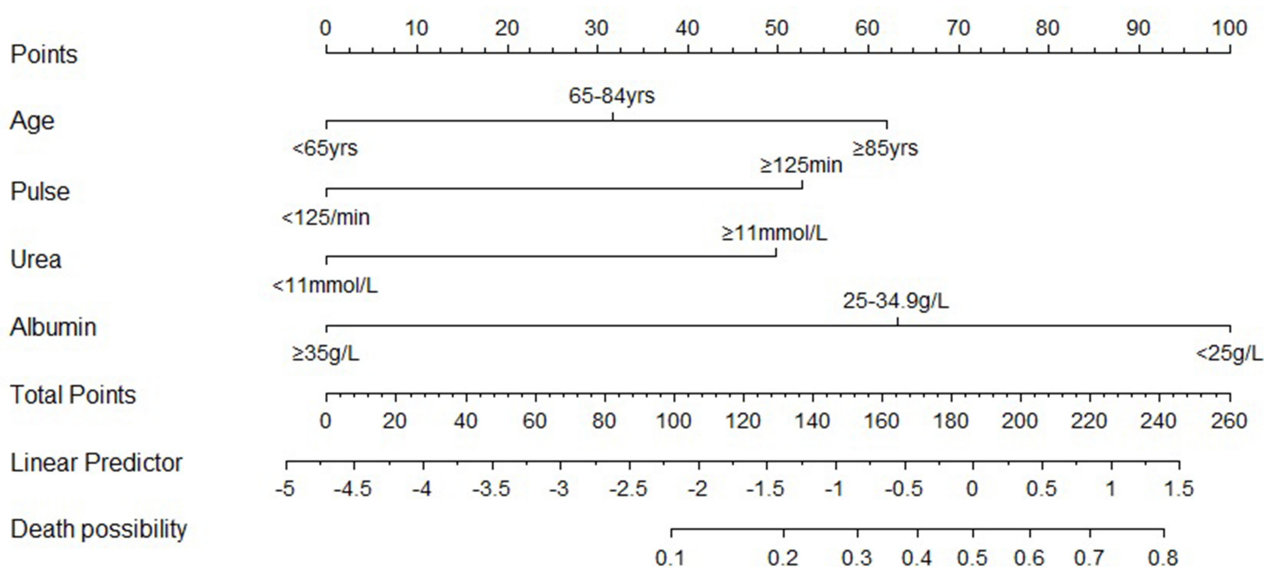


Figure 1 Nomogram for predicting the risk of in-hospital mortality in community-acquired pneumonia patients with type 2 diabetes.

Table 4 The Accuracy of APUA Model, Serum Albumin Alone, CURB-65 and PSI Class for Evaluating the Risk of in-Hospital Mortality in Community-Acquired Pneumonia Patients with Type 2 Diabetes

Variables	AUC (95% CI)	SE	P	P*	P#
Training set (N=359)					
APUA model	0.814(0.770~0.853)	0.034	<0.001		
Albumin	0.695(0.645~0.743)	0.037	<0.001	<0.001	
CURB-65	0.686(0.635~0.733)	0.045	<0.001	0.002	0.864
PSI class	0.710(0.661~0.757)	0.044	<0.001	0.020	0.804
Validation set (N=172)					
APUA model	0.796(0.728~0.854)	0.076	<0.001		
Albumin	0.710(0.636~0.777)	0.072	0.003	0.232	
CURB-65	0.655(0.578~0.725)	0.086	0.073	0.067	0.645
PSI class	0.727(0.654~0.792)	0.057	<0.001	0.343	0.870

Notes: *Compared with APUA model, #Compared with Albumin alone.

Abbreviations: AUC, area under curve; CI, confidence interval; SE, standard error; PSI, pneumonia severity index.

CAP patients on admission, but most patients recovered during follow-up visits.²⁸ The decline of serum albumin during early phase after admission was closely correlated with inflammatory proteins.²⁹ Therefore, the level of serum albumin reflected the degree of inflammatory response. The lower the level of serum albumin, the more severe was the inflammatory response. Second, serum albumin was associated with the severity of infection. Hypoalbuminemia on admission was an independent risk factor for the development of bacteremia, parapneumonic effusion or empyema in patients with CAP.^{30,31} Third, acute cardiac events were significantly associated with in-hospital mortality in CAP patients.

Hypoalbuminemia was a predictor of acute cardiac events.^{32,33}

Some studies have proven that hypoalbuminemia significantly improved the performance of CURB-65 and PSI class for predicting mortality in patients with CAP.^{17,26,34,35} However, CURB-65 and PSI class, particularly PSI class, are complicated scoring systems. Serum albumin makes the systems more complex. In this study, we developed a tool based on serum albumin. After combining with age, pulse and urea, the prognostic performance of serum albumin was increased. The AUCs increased from about 0.7 to about 0.8.

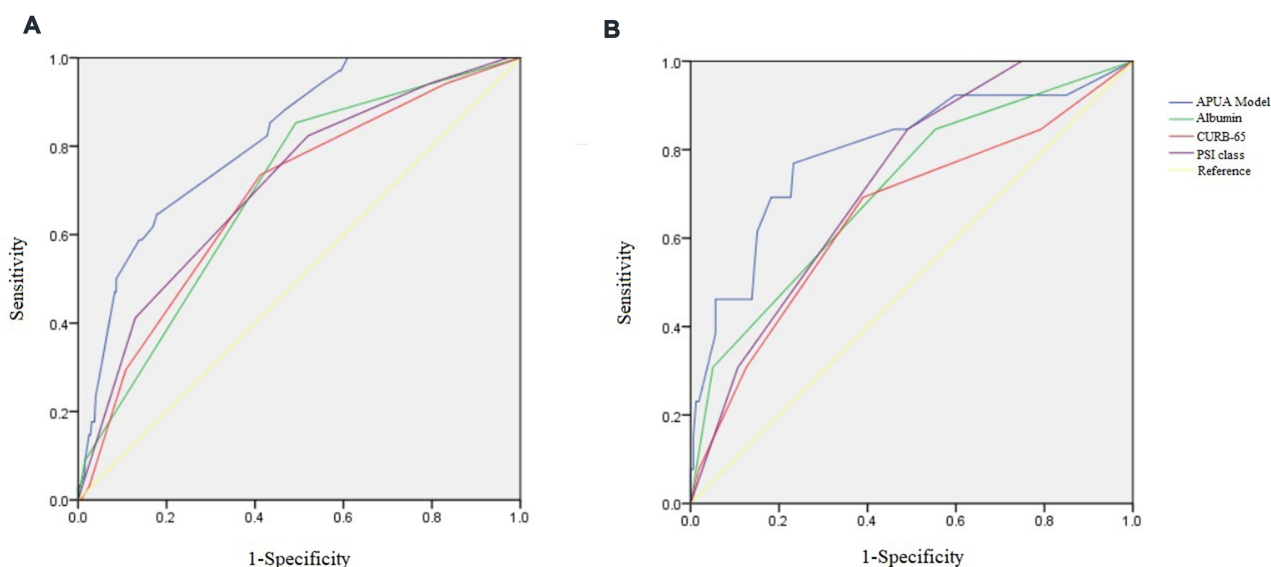


Figure 2 The receiver operator characteristic curve of the APUA model, serum albumin alone, CURB-65 and PSI class for evaluating the risk of in-hospital mortality in community-acquired pneumonia patients with type 2 diabetes. (A) Training set; (B) Validation set.

Table 5 Comparison of Serum Albumin Alone, CURB-65 and PSI Class with The Accuracy of APUA Model for Evaluating the Risk of in-Hospital Mortality in Community-Acquired Pneumonia Patients with Type 2 Diabetes by NRI and IDI

Variables	NRI (95% CI)	P	IDI (95% CI)	P
Training set (N=359)				
Albumin	0.861(0.533~1.189)	<0.001	0.080(0.032~0.127)	0.001
CURB-65	0.766(0.462~1.070)	<0.001	0.087(0.040~0.134)	<0.001
PSI class	0.815(0.493~1.137)	<0.001	0.076(0.023~0.128)	0.005
Validation set (N=172)				
Albumin	0.599(0.041~1.157)	0.035	0.067(-0.033~0.167)	0.188
CURB-65	0.693(0.170~1.216)	0.009	0.109(0.027~0.191)	0.010
PSI class	0.643(0.119~1.166)	0.016	0.086(0.005~0.168)	0.038

Abbreviations: NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval; PSI, Pneumonia Severity Index.

This study had some limitations. First, the level of glucose was similar between dead patients and surviving patients with T2DM. Glucose levels on admission can

predict mortality in patients with CAP without diabetes, but not with diabetes.³⁶ Glycemic gap was associated with mortality in diabetic CAP patients.¹³ Macro and

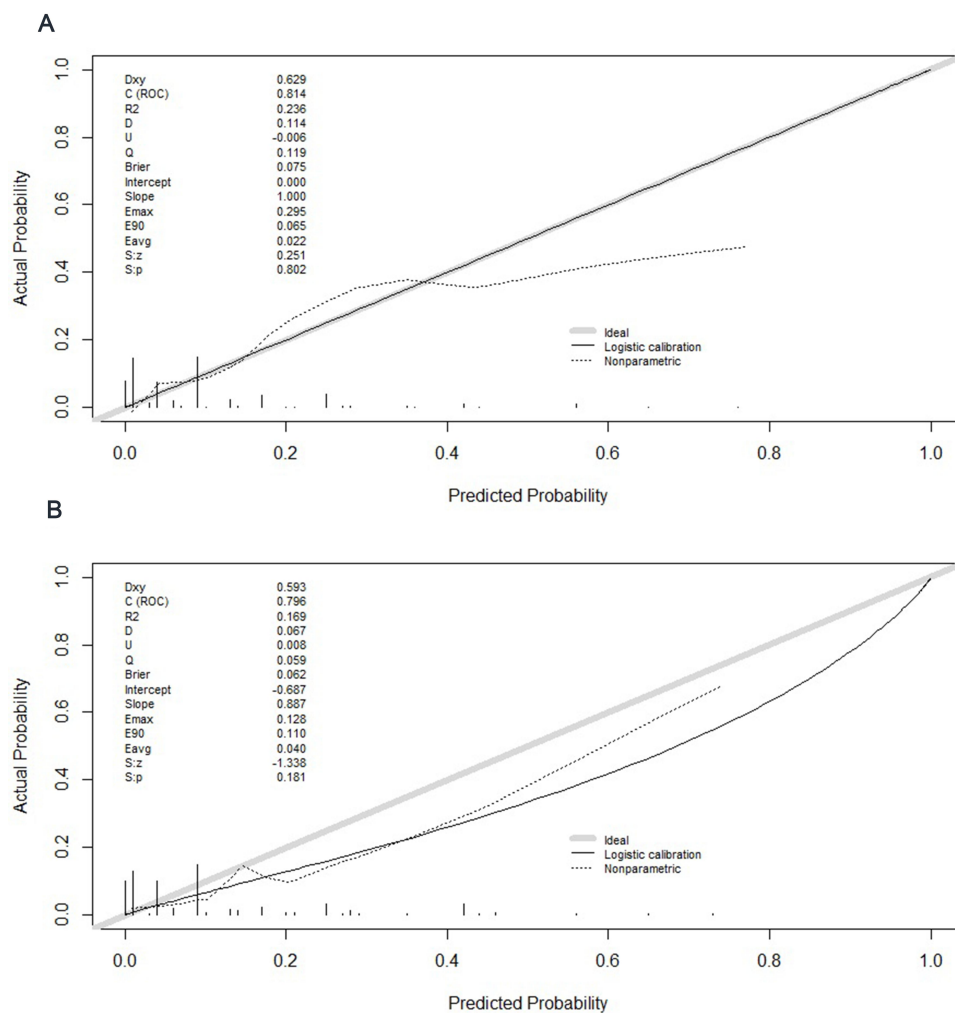


Figure 3 Calibration curves of the APUA model for predicting in-hospital mortality in community-acquired pneumonia patients with type 2 diabetes. (A) Training set; (B) Validation set.

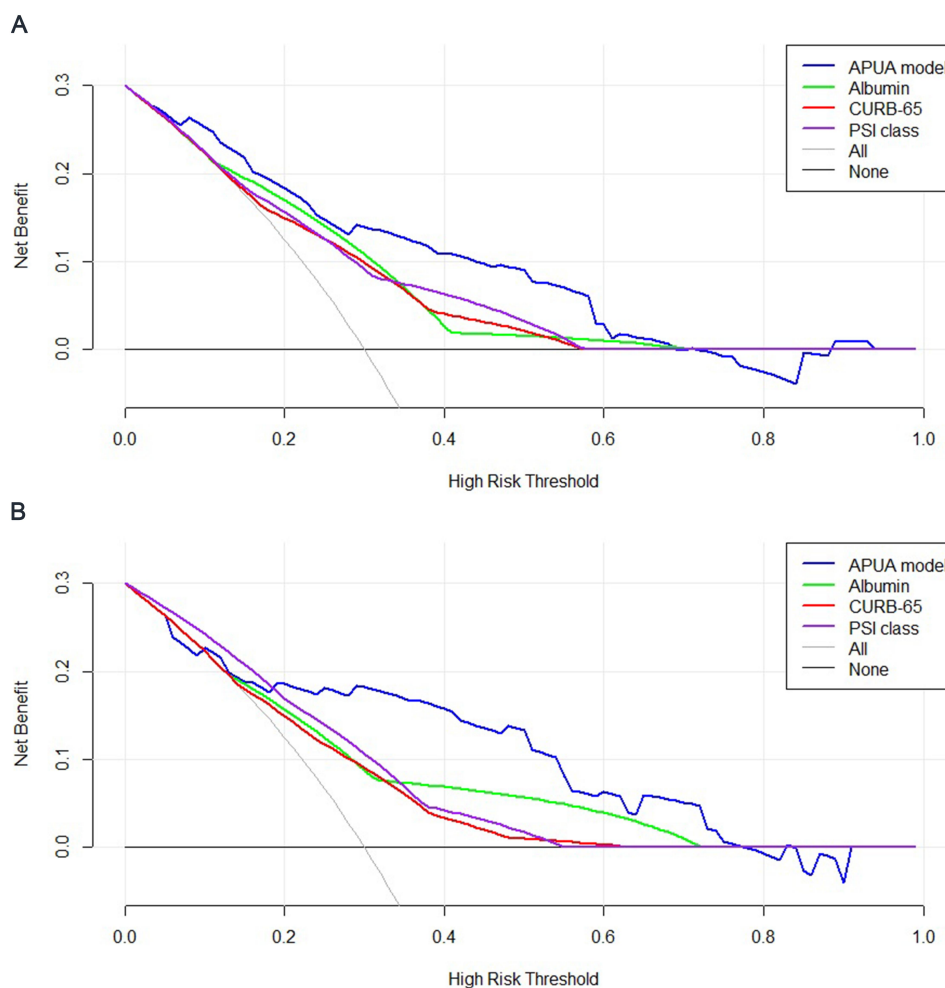


Figure 4 Decision curve analysis of the APUA model for predicting in-hospital mortality in community-acquired pneumonia patients with type 2 diabetes. **(A)** Training set; **(B)** Validation set.

microvascular complications also increased infection-related mortality in patients with T2DM.³⁷ Glycemic gap, micro and macrovascular complications cannot be

quickly identified after admission or tested in primary hospital. Therefore, these potential risk factors were not included in this study. However, the validation of the

Table 6 The Sensitivities, Specificities and Youden's Index of APUA Model in Community-Acquired Pneumonia Patients with Type 2 Diabetes

Predicted Risk	Training Set (N=359)			Validation Set (N=172)			All (N=531)		
	Sen (%)	Spe (%)	Youden's Index	Sen (%)	Spe (%)	Youden's Index	Sen (%)	Spe (%)	Youden's Index
5%	88.2	53.2	0.415	84.6	50.9	0.356	87.2	52.5	0.397
10%	64.7	81.8	0.466	76.9	76.7	0.537	68.1	80.2	0.483
20%	50.0	91.4	0.414	61.5	84.9	0.464	53.2	89.3	0.424
30%	17.6	96.9	0.146	46.2	94.3	0.405	25.5	96.1	0.216
40%	14.7	97.5	0.122	38.5	94.3	0.328	21.3	96.5	0.178
50%	5.9	98.5	0.043	15.4	99.4	0.148	8.5	98.8	0.073

Abbreviations: Sen, sensitivity; Spe, specificity.

Table 7 The Actual Mortality in Patients with Different Predicted Risk of Mortality by APUA Model

Predicted Risk of Mortality	N	Actual Mortality (%)	Model 1		Model 2	
			OR (95% CI)	P	OR (95% CI)	P
0~4.9%	260	2.3	1		1	
5~9.9%	143	6.3	2.843(0.991~8.157)	0.052	2.293(0.764~6.879)	0.139
10~19.9%	51	13.7	6.735(2.162~20.983)	0.001	5.028(1.469~17.206)	0.010
20~29.9%	46	28.3	16.677(5.935~46.857)	<0.001	11.195(3.325~37.699)	<0.001
≥30%	31	38.7	26.737(9.033~79.142)	<0.001	15.039(3.594~62.928)	<0.001

Notes: Model 1: univariate logistic regression analysis. Model 2: multiple logistic regression analysis, adjusted for sex, age and PSI score.

Abbreviations: OR, odds ratio; CI, confidence interval; PSI, pneumonia severity index.

APUA model based on four risk factors demonstrated a good performance. Second, we performed an internal validation in this study, but the validation population was small. So the APUA model should be validated in a larger population.

In summary, the APUA model is a simple and accurate tool for predicting in-hospital mortality of CAP, adapted for patients with T2DM. The predictive performance of the APUA model was better than the CURB-65 and PSI class.

Consent Statement

This was a retrospective study. Data were extracted from the Hospital Information System. We covered patient data confidentiality. Personal information of the patients, such as name and telephone number, were not extracted. So Informed consent was waived by the ethics committee of the First Hospital of Qinhuangdao, and this study complied with the Declaration of Helsinki.

Disclosure

The authors have no relevant funding and conflicts of interest to disclose.

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