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The incremental value of aspartate aminotransferase/alanine aminotransferase ratio combined with CURB-65 in predicting treatment outcomes in hospitalized adult community-acquired pneumonia patients with type 2 diabetes mellitus

Huamei Zhou[1], Xuelei Zhu[1], Yi Zhang[1], Wenjuan Xu[2] and Shiqun Li[3*]

Abstract

Background The features of community-acquired pneumonia (CAP) patients with type 2 diabetes mellitus (T2DM) differ from those without. This study aims to spot a routinely tested parameter with discriminative, predictive and prognostic value to enhance CURB-65's prognostic accuracy in CAP patients with T2DM.

Methods We retrospectively studied consecutive CAP patients from 2020 to 2021, comparing laboratory parameters between patients with and without T2DM. Receiver operating characteristic (ROC) curve analysis, univariate and multivariate logistic regression were used to identify key parameters. The area under the ROC curve (AUC), Fagan's nomogram, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) evaluated the added predictive accuracy.

Results A total of 720 patients were included, comprising 180 diabetic CAP patients and 540 non-diabetic controls after matching for age, gender, and comorbidities through propensity score matching. In diabetic CAP patients, the aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio showed the highest AUC (0.676, 95% CI, 0.575–0.776) among laboratory parameters with different distributions between the groups. AST/ALT was also identified as an independent predictor of poor treatment outcome (OR = 3.672, 95% CI, 1.455–9.268, $p = 0.006$). Adding AST/ALT to CURB-65 slightly increased the AUC, but remarkably enhanced NRI and IDI (AUC, 0.756 vs. 0.782, $p = 0.017$; continuous NRI, 0.635, 95% CI, 0.304–0.966, $p < 0.001$; categorical NRI, 0.175, 95% CI, 0.044–0.307, $p = 0.009$; IDI, 0.043, 95% CI, 0.006–0.080, $p = 0.021$). An AST/ALT ratio of ≥ 1.625 conferred a 74% post-test probability of poor treatment outcome, while < 1.625 predicted 21%. AST/ALT also predicted outcomes for all the CAP patients enrolled (OR = 1.771, 95% CI, 1.231–2.549, $p = 0.002$). Predictive accuracy improved after incorporating AST/ALP into CURB-65 in these population (AUC, 0.615 vs. 0.645, $p = 0.038$; continuous NRI, 0.357, 95% CI, 0.196–0.517, $p < 0.001$; categorical NRI, 0.264, 95% CI, 0.151–0.376, $p < 0.001$; IDI, 0.019, 95% CI, 0.008–0.029, $p < 0.001$).

*Correspondence:
Shiqun Li
lsq254244679@126.com
Full list of author information is available at the end of the article

Conclusions AST/ALT was identified as a discriminative, predictive and prognostic factor for CAP patients with T2DM. The integration of AST/ALT into CURB-65 enhanced outcome prediction for both diabetic and non-diabetic CAP patients.

Keywords Community-acquired pneumonia (CAP), Type 2 diabetes mellitus (T2DM), Prognostic model, Aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT), CUBR-65

Background

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality [1]. Lower respiratory tract infections, including pneumonia, rank as the fourth most common cause of death globally, following ischemic heart disease, stroke, and chronic obstructive pulmonary disease (COPD), and as the most common cause of infectious disease-related mortality worldwide [2]. Age and comorbidities significantly influence the development and outcome of CAP. An U-shaped curve has been noted in CAP incidence that varies by age, and children younger than five years old and older adults are at a high risk [3]. The mortality rates for patients below 65, 65–79, and above 80 were 5%, 8%, and 14%, respectively, and increased to 20%, 42%, and 43% for patients with more than one comorbidity [4]. Conditions such as COPD, cardiovascular disease, cerebrovascular disease, liver disease, renal disease, and diabetes mellitus are widely accepted risk factors for CAP [5]. As the prevalence of diabetes, especially the type 2 diabetes mellitus (T2DM), continues to rise [6–9], it is expected that CAP hospitalization patients, as well as related costs, will also increase [10, 11]. Hospitalized individuals with CAP and T2DM present specific demographic characteristics, clinical manifestations, as well as prognosis. Earlier studies revealed that such individuals are usually older, predominantly male, with more concomitant comorbid conditions and increased rates of pleural effusion [11, 12]. A study that included 227,524 Spanish CAP patients after propensity score matching (PSM) revealed that in-hospital mortality was significantly higher in those without T2DM (14.16% vs. 12.74%, $p<0.001$) [13]. However, another study conducted in China found that the in-hospital mortality of patients with severe CAP and T2DM was higher than that of those without T2DM after PSM (35.2% vs. 31.0%, $p=0.009$) [14]. Studies on long-term survival show some consistency—diabetes is associated with higher mortality rates beyond a 90-day, one-year, and five-year period in patients discharged from CAP [12, 15, 16]. These results underline the variability between the two populations and the intricate nature of the condition. For patients with CAP and concomitant diabetes, a tool to facilitate the initial triage of hospitalized individuals who are at a high risk of poor prognosis is needed to result in better outcomes. A severity evaluation scoring system known as CURB-65, which incorporates new confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years, is commonly employed to evaluate CAP severity. Despite widely used in CAP patients, CURB-65 exhibits unsatisfactory predictive performance in CAP patients with T2DM [17, 18]. The Pneumonia Severity Index (PSI) has shown better performance, but its incorporation of 18 variables in the scoring system makes it more complex than CURB-65 and limits its practicability [19]. This study aims to identify a specific routine blood examination parameter that differs between hospitalized CAP patients with T2DM and those without, demonstrates both predictive and prognostic value, and integrate it into the CURB-65 scoring system to enhance prognosis prediction accuracy for this population. The updated model, designed to be simple and easy to understand with familiar parameters, could be utilized not only by healthcare professionals but also by patients and the general public to better understand the clinical situation.

Methods

Patient selection

The present study is a retrospective analysis conducted in a tertiary hospital, namely The People's Hospital of Nanchuan, Chongqing, China. The study comprised consecutive patients hospitalized for CAP during 2020 and 2021. The diagnostic criteria for CAP were as follows [20]:

A. Onset in community.
B. Relevant clinical manifestations of pneumonia:

(1) New onset of cough or expectoration, or aggravation of existing symptoms of respiratory tract diseases, with or without purulent sputum, chest pain, dyspnea, or hemoptysis;
(2) Fever;
(3) Signs of pulmonary consolidation and/or moist rales;
(4) Peripheral white blood cell count (WBC) > 10×10^9/L or < 4×10^9/L, with or without a nuclear left shift.

C. Chest radiograph showing new patchy infiltrates, lobar or segmental consolidation, ground-glass opacities, or interstitial changes, with or without pleural effusion.

Clinical diagnosis can be established if a patient satisfies Criterion A, Criterion C and any one condition of Criterion B and meanwhile, tuberculosis, pulmonary tumor, noninfectious interstitial lung disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilia and pulmonary vasculitis are all excluded.

Exclusion criteria included patients younger than 18 years old, with radiation pneumonia, aspiration pneumonia, HIV infection, or diabetes mellitus other than type 2 diabetes. Only the first recorded hospital admission during the study period was considered for analysis.

Ethics approval for this retrospective study was obtained from the Ethics Committee of The People's Hospital of Nanchuan, Chongqing (YXYJ-2021–016-01). As data were retrieved from existing medical records, the requirement for informed written consent from individual participants was waived.

Data collection and outcome

Demographic information and comorbidities of patients with CAP were obtained from electronic medical records. Given that diabetes is known to correlate with hematology, inflammatory, and coagulation, while liver, renal and heart conditions are significant risk predictors for CAP as mentioned earlier, laboratory test results of these factors were included as potential variables. Parameters required to calculate the CURB-65 score were also gathered. All aforementioned data were collected within 24 h at admission.

Patients were categorized into two groups based on treatment outcome recorded in medical records— "good prognostic" and "poor prognostic". The "good prognostic" group comprised patients who were cured or showed improvement, while the "poor prognostic" group included those who experienced treatment failure, were discharged against medical advice, or died in hospital. According to the 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association, a patient should meet all of the following criteria to be discharged from the hospital [20], which we refer to as "showed improvement":

(1) normal body temperature for more than 24 h;
(2) heart rate ≤ 100 bpm;
(3) respiratory rate ≤ 24 bpm;
(4) systemic blood pressure ≥ 90 mmHg;
(5) oxygen saturation ≥ 90% (or arterial partial pressure of oxygen ≥ 60 mmHg while breathing room air).

In addition, the patient must be able to receive oral treatment, with no other complications or disturbances of consciousness requiring further management.

For patients classified as 'cured,' in addition to the above-mentioned criteria, all of the following must be met by the time of discharge: clinical symptoms such as cough, sputum production, and chest pain should be largely relieved or completely resolved, body temperature must have remained normal for more than 72 h, and laboratory results, such as white blood cell count, neutrophil percentage, and C-reactive protein levels, should return to normal ranges. Imaging studies, such as chest X-rays or lung CT scans, should show full absorption or significant dissipation of lung lesions, with possible calcification.

Treatment failure is defined by one of the following situations: lack of symptom improvement after initial therapy, requiring a change in antibiotics, or worsening of the condition after initial improvement. Two primary forms of failure are typically observed in clinical practice:

(1) Progressive pneumonia: The disease progresses to acute respiratory failure, requiring mechanical ventilation, or to septic shock, necessitating vasoactive drug therapy within 72 h of hospital admission;
(2) Unresponsiveness to therapy: The patient fails to achieve clinical stability—defined as a body temperature ≤ 37.8℃ and meeting four of the other discharge criteria—72 h after starting initial therapy.

Discharge against medical advice refers to cases where severely ill patients, who meet at least one of the treatment failure criteria, choose to discontinue treatment and leave the hospital.

Diagnosis of T2DM and treatment

T2DM was defined according to the American Diabetes Association guidelines [21]. The diagnosis of T2DM can be established if a patient has a fasting plasma glucose ≥ 7.0 mmol/L, or 2-h plasma glucose ≥ 11.1 mmol/L, or A1c ≥ 6.5%. In addition, a patient with classic symptoms of hyperglycemia or hyperglycemic crisis and a random plasma glucose level ≥ 11.1 mmol/L was also diagnosed with T2DM. Patients who had an established medical history of T2DM based on biochemical diagnosis or those who were newly diagnosed according to the admission parameters in our hospital were identified as T2DM patients.

The antibiotic treatment for CAP followed the consensus guidelines of the Chinese Thoracic Society of Chinese Medical Association for the management of CAP in adults [20], but the specific treatment approach for individual patients was at the discretion of the attending physicians.

Statistical analysis

To balance the differences in age, sex, and concomitant conditions between CAP patients with or without T2DM, and eliminate possible selection bias, a PSM method was used. The comorbidities considered for PSM included hypertension, chronic cardiovascular disease, chronic cerebrovascular disease, other chronic pulmonary disease, chronic hepatic disease, chronic renal disease, and cancer. A PSM ratio of 1:3 was achieved through the "nearest-neighbor" matching method to select statistically matched pairs of CAP patients with or without T2DM and to make the most of the original data.

Missing data were assumed to be at random and were predicted by multiple imputations based on correlations with other observed variables via the mice R package. Only variables with missing values less than 20% were imputed; variables with a missing rate of more than 20% were excluded from the multivariate prognostic analysis [22].

Continuous variables were reported as medians with interquartile ranges (IQRs) and compared using Fisher's exact test. Meanwhile, categorical variables were expressed as frequencies and percentages and compared with the Wilcoxon rank-sum test. The area under the receiver operating characteristic curve (AUC) was used to assess the predictive power of various factors for poor prognosis. Optimal cut-off values were determined using the Youden index. Univariable logistic analysis was performed for each variable, and variables with significant associations ($p<0.05$) were included in the subsequent multivariable logistic analysis to identify independent risk predictors.

AUC, Fagan's nomogram, net reclassification improvement (NRI) (both continuous and categorical), and integrated discrimination improvement (IDI) were employed to evaluate the improved discriminatory ability after the inclusion of additional variables. Fagan's nomogram is a graphical tool that combines a test's likelihood ratio with a patient's pre-test probability of a condition to estimate the post-test probability. The NRI, which calculates the net proportion of correctly reclassified events and the net proportion of correctly reclassified nonevents, was used to quantify the advantage of adding a new predictor to an existing model. Additionally, the IDI, which measures the discrepancy in predicted probabilities in those who do and do not develop poor treatment outcome over all possible probability thresholds, was also utilized to measure the overall improvement.

The Spearman correlation analysis was applied to test the correlation between variables.

All statistical analyses were conducted using R software version 4.2.3. And the TRIPOD + AI guidelines was followed [23].

Results

Sample size, PSM and comparison of laboratory parameters between CAP patients with or without T2DM

In total, 1142 patients with CAP were included in this study, and after excluding 92 patients based on the exclusion criteria, 1050 patients remained. Among them, 180 patients (17.143%) were found to have T2DM, with 146 having an established diagnosis and 34 newly diagnosed. 180 CAP patients with T2DM and 540 matched patients without T2DM after PSM were analyzed.

After PSM for sex, age, and comorbidities, the distribution of these variables showed no significant difference in the two groups of patients, as shown in Table 1 and Fig. S1. Out of the 180 CAP patients with T2DM, 111 were male and 69 were female. The CAP group consisted of 341 males and 199 females. Both groups share a median age of 72 years. Hypertension was the most common comorbidity in these groups, followed by chronic cardiovascular and cerebrovascular diseases.

Table 1 shows the comparison of laboratory parameters between CAP patients with T2DM and their PSM non-diabetic controls. Compared with CAP patients, CAP patients with T2DM had higher white blood cell (WBC, 8.90 vs. 7.80×10^9/L, $p=0.006$), neutrophil (NEU, 7.12 vs. 6.15×10^9/L, $p=0.007$), and lymphocyte (LYM, 1.21 vs. 0.94×10^9/L, $p=0.001$). Despite the original platelet, lymphocyte and neutrophil counts, platelet-lymphocyte ratio (PLR) and neutrophil–lymphocyte ratio (NLR) were investigated, as they are associated with the prognosis of patients with CAP [24, 25]. PLR was lower in CAP patients with T2DM (162.18 vs. 200.23, $p=0.022$), while NLR showed no difference (6.40 vs. 6.66, $p=0.776$). There is no difference in terms of infection and inflammation indices between these two groups. As expected, CAP patients with T2DM had significantly higher blood glucose (GLU) levels (10.33 vs. 5.77 mmol/L, $p<0.001$) and glycated hemoglobin A1c (HbA1c) levels (7.80 vs. 5.90%, $p<0.001$). In terms of coagulation, activated partial thromboplastin time (APTT) was shortened for those with T2DM (34.75 vs. 36.70 s, $p=0.010$).

Blood potassium level, which reflects renal function, was found slightly higher in patients with T2DM (K, 3.94 vs. 3.84 mmol/L, $p=0.049$). Regarding biochemical markers of liver function, CAP patients with T2DM had lower aspartate aminotransferase (AST, 21.00 vs.

Table 1 Clinical characteristics of CAP and CAP-T2DM patients

Variables	CAP *n* = 540	CAP-T2DM *N* = 180	*p* value
Gender (male %)	341 (63.1)	111 (61.7)	0.723
Age (years)	72.00 (62.00, 79.00)	72.00 (63.00, 78.00)	0.587
Comorbidities, n (%)			
Hypertension	191 (35.4)	67 (37.2)	0.655
Chronic Cardiovascular Diseases	127 (23.5)	44 (24.4)	0.840
Chronic Pulmonary Diseases	51 (9.4)	21 (11.7)	0.391
Chronic Cerebrovascular Diseases	83 (15.4)	31 (17.2)	0.557
Chronic Hepatic Diseases	12 (2.2)	6 (3.3)	0.413
Chronic Renal Diseases	17 (3.1)	7 (3.9)	0.634
Cancer	27 (5.0)	11 (6.1)	0.566
Complete blood count			
WBC ($\times 10^9$/L)	7.80 (5.80, 11.70)	8.90 (6.50, 13.02)	0.006
NEU ($\times 10^9$/L)	6.15 (4.10, 10.01)	7.12 (4.92, 10.79)	0.007
LYM ($\times 10^9$/L)	0.94 (0.60, 1.40)	1.21 (0.71, 1.76)	0.001
PLT ($\times 10^9$/L)	180.00 (130.00, 252.00)	186.50 (135.00, 251.75)	0.364
HB (g/L)	120.00 (106.00, 131.50)	117.00 (101.00, 133.00)	0.376
NLR	6.66 (3.33, 13.71)	6.40 (3.73, 11.87)	0.776
PLR	200.23 (121.28, 323.08)	162.18 (104.29, 294.09)	0.022
Infection and inflammation			
ESR (mm/h)	45.00 (21.00, 72.50)	56.00 (27.00, 89.50)	0.059
PCT (ug/L)	0.17 (0.10, 0.84)	0.18 (0.10, 0.83)	0.470
CRP (mg/L)	36.74 (8.96, 104.38)	37.03 (8.00, 110.82)	0.947
Blood glucose condition			
GLU (mmol/L)	5.77 (5.02, 7.09)	10.33 (7.24, 14.99)	< 0.001
HbA1c (%)	5.90 (5.60, 6.30)	7.80 (6.80, 10.30)	< 0.001
Coagulation			
APTT (sec)	36.70 (32.30, 40.80)	34.75 (31.30, 39.30)	0.010
FIB (g/L)	4.26 (3.26, 5.79)	4.42 (3.39, 5.79)	0.272
PT (sec)	13.70 (12.90, 14.70)	13.80 (12.90, 14.60)	0.861
INR	1.08 (1.02, 1.17)	1.09 (1.01, 1.17)	0.705
TT (sec)	17.55 (16.70, 18.72)	17.60 (16.80, 18.70)	0.615
Renal function			
BUN (mmol/L)	5.76 (4.31, 8.10)	5.78 (4.44, 8.87)	0.507
CREA (umol/L)	73.35 (59.00, 92.55)	71.70 (54.92, 97.53)	0.296
UA (umol/L)	300.30 (229.00, 383.50)	292.60 (228.25, 376.70)	0.916
A1MG (mg/L)	26.90 (21.50, 36.58)	31.60 (22.10, 43.55)	0.235
B2MG (mg/L)	2.70 (1.86, 4.65)	2.69 (1.92, 4.11)	0.872
Ca (mmol/L)	2.17 (2.07, 2.28)	2.20 (2.07, 2.31)	0.092
Cl (mmol/L)	105.80 (103.00, 108.10)	105.00 (101.50, 108.10)	0.187
K (mmol/L)	3.84 (3.48, 4.19)	3.94 (3.60, 4.25)	0.049
Mg (mmol/L)	0.87 (0.80, 0.94)	0.86 (0.78, 0.93)	0.118
Na (mmol/L)	139.10 (136.35, 141.80)	139.00 (136.00, 142.00)	0.955
P (mmol/L)	0.97 (0.83, 1.16)	0.96 (0.82, 1.13)	0.615
Liver function			
ALT (U/L)	18.00 (11.00, 33.00)	18.00 (12.00, 30.00)	0.909
AST (U/L)	25.00 (19.00, 38.00)	21.00 (15.00, 35.75)	0.001
AST/ALT	1.42 (1.06, 2.00)	1.22 (0.94, 1.62)	0.001
5'-NT (U/L)	5.10 (3.20, 8.05)	5.85 (3.30, 10.40)	0.043
ADA (U/L)	11.90 (9.30, 16.00)	15.30 (12.12, 20.20)	< 0.001

Table 1 (continued)

Variables	CAP *n* = 540	CAP-T2DM *N* = 180	*p* value
ALP (U/L)	84.00 (69.50, 106.00)	96.50 (75.25, 128.00)	0.001
CHE (U/L)	5712.00 (4442.00, 7104.50)	6035.00 (4968.75, 7816.25)	0.011
GGT (U/L)	26.00 (17.00, 56.00)	34.00 (21.25, 64.00)	0.019
LDH (U/L)	220.00 (185.00, 288.75)	217.50 (174.00, 291.50)	0.237
MAO (U/L)	10.40 (7.90, 14.90)	10.10 (7.18, 14.40)	0.443
TP (g/L)	64.90 (59.90, 69.88)	65.05 (59.73, 70.70)	0.614
PA (mg/L)	152.00 (109.50, 195.00)	152.00 (109.75, 195.00)	0.608
ALB (g/L)	35.00 (31.20, 38.50)	34.30 (30.50, 38.55)	0.487
GLOB (g/L)	29.35 (25.80, 32.90)	29.90 (26.20, 33.98)	0.174
A/G	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)	0.119
TBA (umol/L)	4.30 (2.30, 7.40)	3.55 (2.20, 6.80)	0.307
CG (mg/L)	1.70 (1.20, 2.73)	1.85 (1.30, 2.40)	0.618
TBIL (umol/L)	11.20 (8.00, 16.10)	11.10 (6.93, 15.88)	0.470
DBIL (umol/L)	3.40 (2.50, 5.70)	3.40 (2.30, 5.40)	0.394
Cardiac and myocardial condition			
NT-proBNP (pg/ml)	851.05 (226.22, 2554.76)	803.60 (210.90, 2891.38)	0.752
CK-MB (U/L)	1.51 (0.99, 2.80)	1.46 (0.90, 2.63)	0.458
Mb (ng/ml)	78.46 (44.63, 176.20)	79.39 (52.38, 170.28)	0.851
cTnI (μg/L)	0.02 (0.00, 0.05)	0.02 (0.00, 0.06)	0.558
CK (U/L)	95.00 (56.00, 211.00)	81.00 (45.00, 133.50)	0.023
IMA (U/mL)	80.30 (77.00, 85.70)	80.70 (76.75, 84.35)	0.675
CURB-65 score, n (%)			
0–1	270 (50.2)	90 (50.0)	1.000
2	185 (34.4)	58 (32.2)	0.649
3–5	83 (15.4)	32 (17.8)	0.482
CURB-65 (points)	1.00 (1.00, 2.00)	1.50 (1.00, 2.00)	0.770
LOS (days)	6.00 (4.00, 10.00)	9.00 (6.00, 13.25)	< 0.001

Data are presented as frequency (%) or as median (interquartile range)

CAP community-acquired pneumonia, *CAP-T2DM* community-acquired pneumonia with type 2 diabetes mellitus, *WBC* white blood cell, *NEU* neutrophil, *LYM* lymphocyte, *PLT* platelet, *HB* hemoglobin, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *CRP* C-reactive protein, *GLU* glucose, *HbA1c* glycated hemoglobin, *A1c APTT* activated partial thromboplastin time, *FIB* fibrinogen, *PT* prothrombin time, *INR* international normalized ratio, *TT* thrombin time, *BUN* blood urea nitrogen, *CREA* creatinine, *UA* uric acid, *A1MG* α1-microglobulin, *B2MG* β2-microglobulin, *Ca* calcium, *Cl* chlorine, *K* potassium, *Mg* magnesium, *Na* sodium, *P* phosphorus, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AST/ALT* aspartate aminotransferase/alanine aminotransferase ratio, *5'-NT* 5-nucleotidase, *ADA* adenosine deaminase, *ALP* alkaline phosphatase, *CHE* acetylcholine esterase, *GGT* γ-glutamyltransferase, *LDH* lactate dehydrogenase, *MAO* monoamine oxidase, *TP* total protein, *PA* prealbumin, *ALB* albumin, *GLOB* globulin, *A/G* albumin/globulin ratio, *TBA* total bile acid, *CG* cholyglycine, *TBIL* total bilirubin, *DBIL* direct bilirubin, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *CK-MB* MB isoenzyme of creatine kinase, *Mb* myohemoglobin, *cTnI* cardiac troponin I, *CK* creatine kinase, *IMA* ischemia-modified albumin, *LOS* length of stay

25.00 U/L, $p=0.001$) and aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT, 1.22 vs. 1.42, $p=0.001$) compared to their non-diabetic counterparts. Additionally, they had higher levels of 5'-nucleotidase (5'-NT, 5.85 vs. 5.10 U/L, $p=0.043$), adenosine deaminase (ADA, 15.30 vs. 11.90 U/L, $p<0.001$), alkaline phosphatase (ALP, 96.50 vs. 84.00 U/L, $p=0.001$), acetylcholine esterase (CHE, 6035.00 vs.5712.00 U/L, $p=0.011$), and γ-glutamyltransferase (GGT, 34.00 vs. 26.00 U/L, $p=0.019$). Myocardial enzyme creatine kinase (CK) was also lower in CAP patients with T2DM (81.00 vs. 95.00 U/L, $p=0.023$).

CAP patients with concomitant T2DM experienced a prolonged length of stay (LOS) in our hospital (9.00 vs. 6.00 days, $p<0.001$). There was no difference between the two groups of people in terms of CURB-65.

Predictive value of indicators for treatment outcome

To evaluate the predictive variables of treatment outcome that displayed differences between CAP patients with T2DM and their matched controls, receiver-operating characteristic (ROC) curves were utilized and the results are presented in Table 2. Among the parameters analyzed, AST/ALT had the highest predictive value

Table 2 Predictive ability of laboratory indices for forecasting treatment outcome for CAP-T2DM patients

Variables	AUC	Cut-off value	Youden index	Sensitivity	Specificity	PPV	NPV
AST/ALT	0.676 (0.575–0.776)	1.625	0.336	0.500	0.836	0.476	0.848
WBC	0.647 (0.549–0.745)	10.700	0.289	0.585	0.704	0.375	0.848
CK	0.635 (0.523–0.747)	81.000	0.255	0.688	0.568	0.386	0.821
LYM	0.594 (0.487–0.700)	0.863	0.272	0.561	0.711	0.371	0.842
PLR	0.579 (0.467–0.691)	191.821	0.276	0.634	0.642	0.351	0.851
ADA	0.577 (0.470–0.684)	18.550	0.200	0.500	0.700	0.339	0.820
GGT	0.564 (0.443–0.684)	28.000	0.154	0.750	0.404	0.300	0.826
APTT	0.557 (0.452–0.663)	33.150	0.164	0.500	0.664	0.323	0.806
GLU	0.556 (0.445–0.668)	9.980	0.159	0.647	0.512	0.268	0.840
5′-NT	0.533 (0.426–0.640)	13.100	0.121	0.275	0.846	0.355	0.791
CHE	0.520 (0.400–0.639)	8109.500	0.118	0.281	0.837	0.375	0.770
K	0.519 (0.412–0.625)	4.045	0.107	0.463	0.644	0.288	0.794
ALP	0.518 (0.389–0.647)	136.500	0.205	0.344	0.862	0.458	0.794

CAP-T2DM community-acquired pneumonia with type 2 diabetes mellitus, *AUC* area under the receiver operating characteristic curve, *PPV* positive predictive value, *NPV* negative predictive value, *AST/ALT* aspartate aminotransferase/alanine aminotransferase ratio, *WBC* white blood cell, *CK* creatine kinase, *LYM* lymphocyte, *PLR* platelet-lymphocyte ratio, *ADA* adenosine deaminase, *GGT* γ-glutamyltransferase, *APTT* activated partial thromboplastin time, *GLU* glucose, *5′-NT* 5-nucleotidase, *CHE* acetylcholine esterase, *K* potassium, *ALP* alkaline phosphatase

Table 3 Independent variables for treatment outcome in CAP patients with T2DM

Variables	Comparison groups	Odds ratio	95% CI	*p* value
CURB-65 (points)	2 vs. 0–1	6.349	2.194–18.374	0.001
	3–5 vs. 0–1	10.037	3.051–33.015	< 0.001
PLR	≥ 191.821 vs. < 191.821	4.541	1.857–11.107	0.001
AST/ALT	≥ 1.625 vs. < 1.625	3.672	1.455–9.268	0.006
WBC ($\times 10^9$/L)	≥ 10.7 vs. < 10.7	3.270	1.341–7.976	0.009

Adjusted for gender, age, comorbidities, and other biomarkers

CAP community-acquired pneumonia, *T2DM* type 2 diabetes mellitus, *PLR* platelet-lymphocyte ratio, *AST/ALT* aspartate aminotransferase/alanine aminotransferase ratio, *WBC* white blood cell

with an AUC of 0.676 (95% CI, 0.575–0.776), followed by WBC and CK, (AUC of WBC: 0.647, 95% CI, 0.549–0.745; AUC of CK: 0.635, 95% CI, 0.523–0.747). Any parameters with an AUC of less than 0.5, indicating a lack of discriminative ability, were not shown in the table. The optimal cutoff values were determined using the Youden Index.

Independent risk predictors for treatment outcome

Candidate variables to be added to CURB-65 were chosen by identifying those who exhibited differences between the two sets (indicating their discriminative value) and simultaneously showed an AUC > 0.5 (indicating their predictive value). For patients with both CAP and T2DM, univariable and multivariable logistic analysis were performed with candidate variables dichotomized according to optimal cutoff values while keeping other variables treated as continuous variables. The results of univariate logistic regression can be found in Additional file1: Table S1. And the following were significant predictors of treatment outcome: CURB-65 (CURB-65 = 2 vs. 0–1: OR = 6.349, 95% CI, 2.194–18.374, $p = 0.001$; CURB-65 = 3–5 vs. 0–1: OR = 10.037, 95% CI, 3.051–33.015, $p < 0.001$), PLR (OR = 4.541, 95% CI, 1.875–11.107, $p = 0.001$), AST/ALT (OR = 3.672, 95% CI, 1.455–9.268, $p = 0.006$), and WBC (OR = 3.270, 95% CI, 1.341–7.976, $p = 0.009$) (Table 3).

Predictive efficacy of the chosen variable in combination with CURB-65 to differentiate treatment outcome

AST/ALT was then chosen as the variable to combine with CURB-65 after integrated consideration of discrimination, prediction as well as prognosis ability among the candidate parameters. The predicted probability of the outcome event can be calculated using the following formula:

Probability = 1/(1 + exp(-(−2.684 + 1.568 × CURB-65 (2 points) + 2.277 × CURB-65 (3—5 points) + 1.084 × AST/ALT (≥ 1.625)))). Comparing with CURB-65 alone, combination with AST/ALT yielded an improvement of AUC

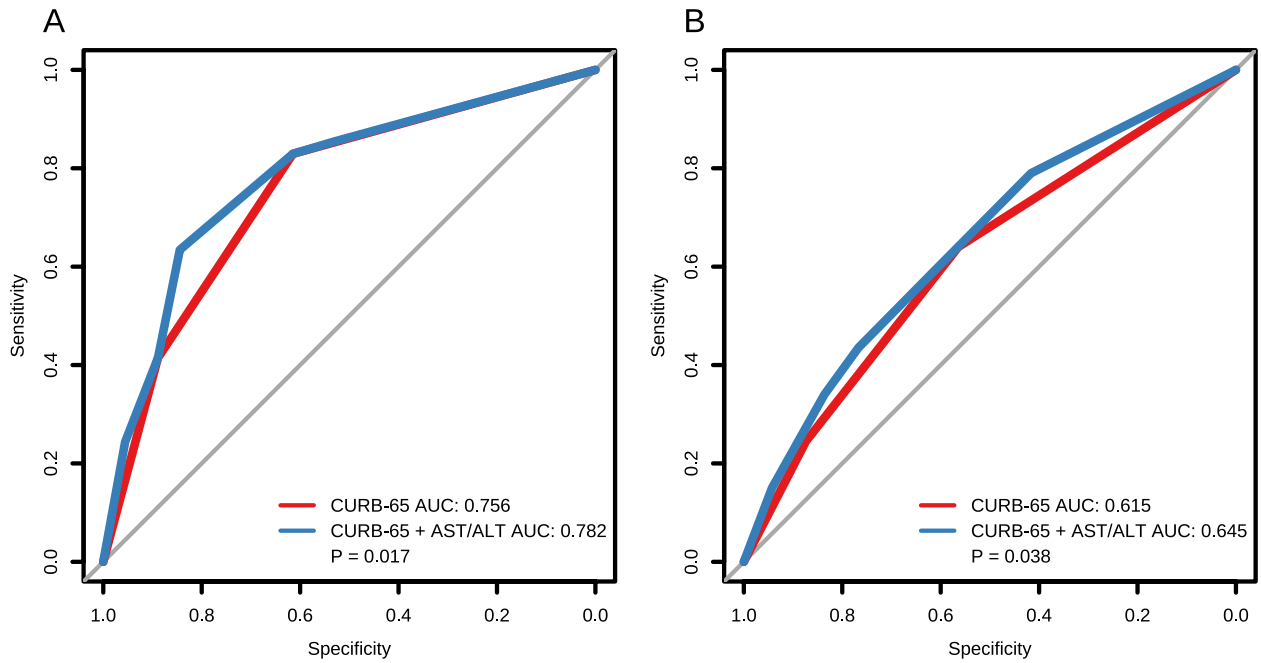

Fig.1 ROC analysis for treatment outcome prediction. AUCs indicate the predictive performance before and after incorporating ASTL/ALT into CURB-65 in CAP patients with T2DM (A) and in all the CAP patients enrolled in this study (B)

(AUC of CURB-65 alone: 0.756, 95% CI, 0.677–0.835; AUC of CURB-65 + AST/ALT: 0.782, 95% CI, 0.700–0.863; $p = 0.017$; Fig. 1A). In Fagan's nomogram, the pretest probability of poor treatment outcome based on CURB-65 was 40% (which may vary depending on different settings). The positive likelihood ratio (LR+) of test AST/ALT was 4.36, and the negative likelihood ratio (LR-) was 0.41 (Fig. 2A). If one CAP patients with T2DM has an AST/ALT ratio of ≥ 1.625, the probability of experiencing a poor treatment outcome would rise up to 74%. In contrast, an AST/ALT ratio of < 1.625 was linked to a 21% probability of the same outcome. This indicates a noteworthy change in probability before and after incorporating the AST/ALT ratio. Meanwhile, the NRI and IDI, which were both originally designed to quantify the incremental risk prediction value after adding a novel factor, revealed the discriminative ability enhanced significantly after combination the specific parameter (continuous NRI, 0.635, 95% CI, 0.304–0.966, $p < 0.001$; categorical NRI, 0.175, 95% CI, 0.044–0.307, $p = 0.009$; IDI, 0.043, 95% CI, 0.006–0.080, $p = 0.021$).

The reclassification table, presented in Additional File 1: Table S2, illustrates the categorical NRI, which plays significant role in interpreting the clinical impact of risk reclassification and its potential influence on clinical practice. Among the 41 patients with poor treatment outcomes, 9 showed improved classification using the model with the AST/ALT ratio, and none experienced worsened classification, yielding an event NRI of 0.219. Among the 135 patients with good treatment outcomes, no classification improved with the augmented model, while 6 patients experienced worsened classification, resulting in a nonevent NRI of −0.044. Therefore, the categorical NRI, calculated as the sum of the event and nonevent NRIs, was 0.175 and statistically significant ($p = 0.009$).

Correlation of AST/ALT and other parameters in CAP patients with T2DM

Table S3 in Additional file 1 presented the parameters that exhibit a significant correlation with AST/ALT in CAP patients with T2DM, while the full Spearman correlation analysis result is listed in Table S4. In this patient population, AST/ALT demonstrated a positive correlation with female gender, age ($r = 0.317$, $p < 0.001$), hypertension ($r = 0.228$, $p = 0.003$), chronic hepatic diseases ($r = 0.157$, $p = 0.039$), and CURB-65 ($r = 0.265$, $p < 0.001$). Furthermore, higher AST/ALT was significantly associated with lower hemoglobin, reduced average blood glucose of the past three months, prolonged coagulation time, and elevated levels of myocardial enzymes besides of other indices of liver function.

Predictive value of AST/ALT in all the CAP patients

Upon adjusting for confounders, AST/ALT was found to be an independent risk factor for poor treatment outcome in all 720 CAP patients included in this research,

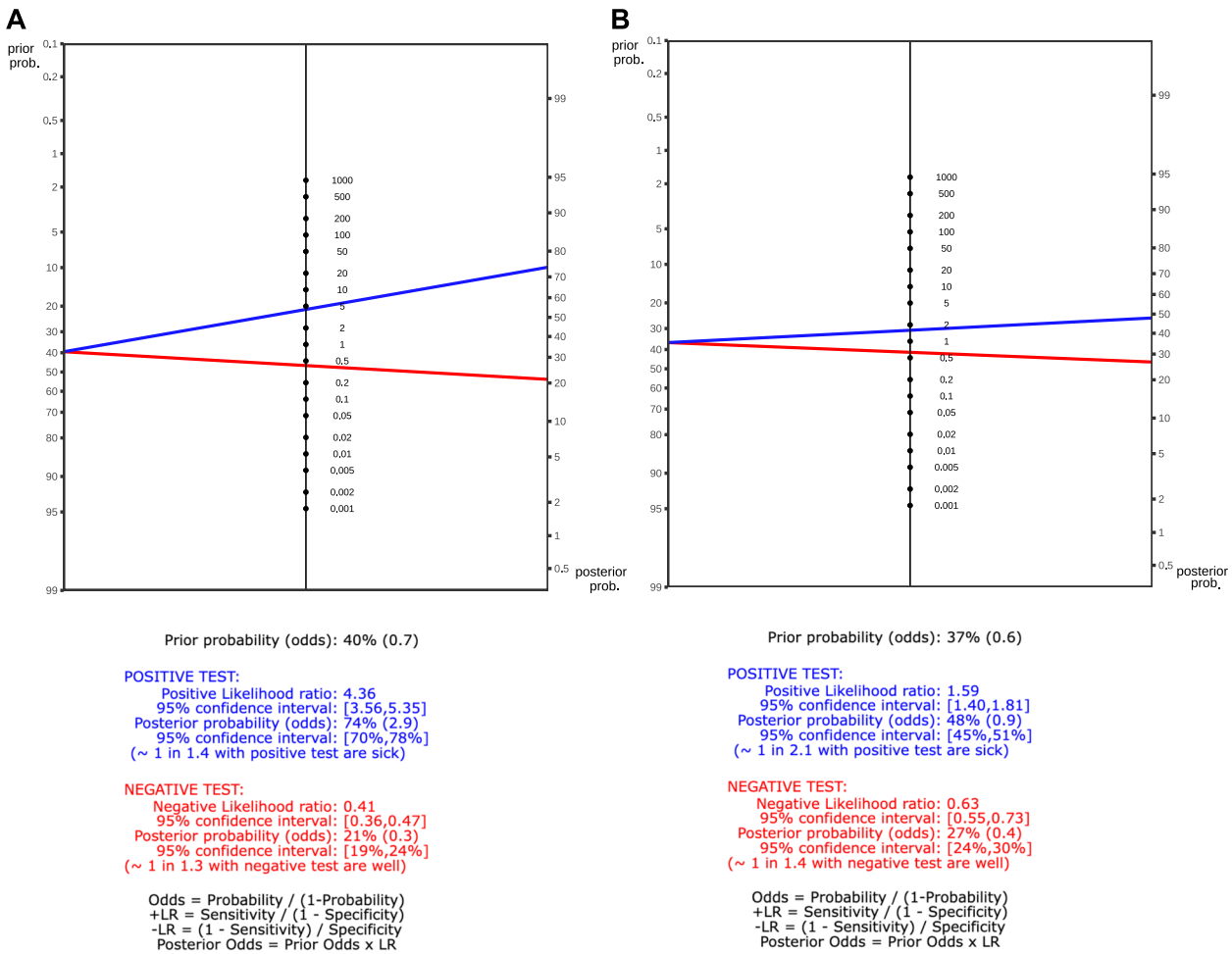

Fig.2 Fagan's nomogram. Fagan's nomogram shows the posterior probability of poor treatment outcome after incorporating AST/ALT into CURB-65 in CAP patients with T2DM (A) and in all the CAP patients enrolled in this study (B). The left axis represents the pre-test probability, which varies across cohorts. The middle axis indicates the positive and negative likelihood ratios, while the right axis shows the post-test probability. To calculate the risk (post-test probability, %) of poor prognosis for an individual patient, a straight line can be drawn through the pre-test probability and the positive (blue line) or the negative likelihood ratio (red line) to yield a post-test probability. All corresponding data are listed below

with an OR of 1.771 (95% CI, 1.231–2.549, $p=0.002$, Table S5, S6). Again, combination of CURB-65 and AST/ALT yielded an advancement in terms of AUC (AUC of CURB-65 alone: 0.615, 95% CI, 0.572–0.658; AUC of CURB-65 + AST/ALT: 0.645, 95% CI, 0.601–0.689, $p=0.038$; Fig. 1B), NRI (continuous NRI, 0.357, 95%CI, 0.196–0.517, $p<0.001$; categorical NRI, 0.264, 95% CI, 0.151–0.376, $p<0.001$), and IDI (0.019, 95% CI, 0.008–0.029, $p<0.001$), which indicates that the addition of AST/ALT to the CURB-65 score in patients with CAP will lead to a prominently improvement in predictive accuracy. In the case of Fagan's nomogram, adding the AST/ALT ratio to the CURB-65 score slightly altered the posterior probability of treatment prognosis. The prior probability was 37% in this cohort, and an AST/ALT ratio of ≥ 1.625 gave a post-test probability of 48% for poor treatment outcome, an AST/ALT ratio of <1.625 had a 27% probability of the same outcome (Fig. 2B).

Discussion

In this study, we aimed to enhance the accuracy of the CURB-65 score in predicting treatment outcomes for CAP patients with T2DM by adding a routine examination index. To identify a suitable variable to combine with the CURB-65 score, we compared laboratory indices between patients with and without T2DM matched for age, sex, and comorbidities. Variables with prediction

and prognosis value were identified using AUC calculations and multivariable logistic regression. The AST/ALT ratio was subsequently selected given its discriminative, predictive as well as prognostic merits. The incorporation of the AST/ALT ratio into CURB-65 considerably improve the performance of the CURB-65 assessment for those CAP patients with concomitant T2DM. Notably, our analysis also revealed that AST/ALT ratio could serve as an independent predictor of poor treatment outcome in 720 CAP patients enrolled in our research, regardless of whether they have diabetes mellitus. The combination of AST/ALT and CURB-65 also offers benefits to these patients.

Besides its infectious nature, CAP also triggers significant systemic responses, which may classify this condition as inflammatory. This is evidenced by the systemic release of considerable amounts of proinflammatory cytokines and lipid mediators [26]. The PLR has demonstrated an association with systemic inflammation and serves as a biomarker of infection. Its clinical significance has been showed in various diseases, including CAP [24, 27, 28]. In this study, it was found that incorporating the PLR into CURB-65 did not improve the diagnostic accuracy of CURB-65 in the context of CAP (Fig. S2). This result is in line with previous research [25]. Meanwhile, another inflammatory factor, NLR, showed no difference in CAP patients with and without T2DM, and was not identified as an independent prognostic predictor for those with T2DM. The incorporation of NLR into prognosis analysis for CAP patients is an emerging trend, and currently, only two studies have validated its potential value in CAP patients with T2DM [24, 25]. More research is warranted to address the discrepancy between previous studies and our findings.

Elevated ALT/AST ratio, measured as the ratio of alanine aminotransferase to aspartate aminotransferase, which is the reciprocal of AST/ALT in our study, was found to be strongly correlated with an increased incidence of nonalcoholic fatty liver disease (NAFLD) in non-obese Chinese individuals [29]. NAFLD is a metabolic disorder characterized by insulin resistance, similar to diabetes. A large-scale retrospective analysis demonstrated that diabetes development was more likely to occur in individuals with a lower AST/ALT ratio (≤ 1.18) [30]. This ratio closely resembled the mean AST/ALT level seen in CAP patients with T2DM in our study, which was measured at 1.22. This finding leads us to hypothesize that the lower AST/ALT ratio observed in the diabetes group in the present study may be attributed to the such relationship between this ratio and T2DM. This correlation may be partly explained by the negative association between AST/ALT ratio and the average blood glucose levels, as found in our study (r for AST/ALT and HbA1c: -0.176, $p=0.042$), and the negative association between the ratio and insulin resistance index discovered by other research [31]. NAFLD has been associated with elevated levels of ADA, ALP, CHE, and GGT, indicating relatively reduced liver function [32–34]. This may explain the higher levels of these biomarkers in CAP-T2DM patients compared to CAP patients in our study. It is worth noting that the NAFLD population is not only at a higher risk of infection but also experiences a more complicated and prolonged course of infection and a poor outcome due to impaired liver immunologic function [35]. Given that NAFLD is an emerging field of research, only a few studies identified the relationship between NAFLD and the prognosis of CAP patients. The intersection of NAFLD, T2DM, and CAP remains largely unexplored in scientific research. Further research in this area could provide valuable insight into the prognostic potential of the AST/ALT ratio in CAP patients with T2DM.

To the best of our knowledge, this is the first study to identify AST/ALT as a predictor of treatment outcome for patients with T2DM and CAP. Meanwhile, a higher AST/ALT ratio was found to be positively correlated with age and hypertension in this population, both are well-established risk factors for cardiovascular disease (CVD) in diabetic patients [36]. Notably, AST/ALT per se is closely associated with CVD in both the general population and patients with diabetes. A Japanese study involving 3,494 participants reported that a high AST/ALT ratio was independently associated with all-cause and CVD mortality [37]. Similarly, a 6-year follow-up study conducted in Italy revealed that the AST/ALT ratio was an remarkable risk factor for all-cause and CVD mortality in patients with diabetes [38]. Previous research showed that participants with a high AST/ALT ratio had an elevated prevalence of pre-existing CVD than those with a lower ratio, indicating heart damage and overload, along with underlying CVD episodes, which could lead to poor prognosis [37]. This may explain the result found in the study that a higher AST/ALT ratio was positively correlated with myocardial injury biomarkers, implying that the ratio probably is a valuable prognostic factor for CAP patients.

In addition to being an infectious disease, CAP can also cause hemostasis disorders, which can be demonstrated by increased coagulation [26]. The probability of death increased with the rise in baseline coagulation biomarker levels, indicating their potential to serve as markers for severe CAP [39]. This is further supported by another study, which found significant differences in coagulation biomarkers between patients with severe CAP and those with milder cases [40]. In T2DM patients, endothelial dysfunction, coagulative activation, impaired fibrinolysis,

and hyper-reactive platelets contribute to the diabetic prothrombotic state, which is strongly associated with macrovascular complications [41]. The positive relationship between prolonged coagulation time and AST/ALT may clarify the importance of this ratio and establish its association with coagulation and CVD in the context of CAP and T2DM. Additionally, the AST/ALT's significance is highlighted by its link with CURB-65, indicating its ability to determine the severity of CAP patients.

Using the Fagan's nomogram derived in our study, along with a pre-test probability previously obtained, enables healthcare professionals to quickly assess the risk of individual diabetic CAP patients at the bedside. A large positive value of the event NRI from our findings (Table S2) indicates that the AST/ALT ratio assists in identifying diabetic CAP patients at higher risk of poor treatment outcomes. Emphasizing the significance of the AST/ALT ratio enables clinicians to pay attention to this parameter, providing more intensive care to these patients, which may lead to improved outcomes. This approach is cost-effective, as assessing the AST/ALT ratio is already a routine part of clinical practice for evaluating liver function upon admission. The nonevent NRI was −0.044, indicating that the addition of the AST/ALT ratio to the CURB-65 scoring system worsens its classification ability. None of the 135 patients with good treatment outcomes were assigned to a lower risk category, while 6 were classified into a higher risk category. Although this model may misclassify some low-risk patients as high-risk, potentially resulting in the waste of medical resources, this probability is relatively low. Given the potential benefits for patients with poor prognosis, we still believe this model holds significant clinical importance, and incorporating the AST/ALT ratio into the CURB-65 score could help alleviate the overall disease burden. Moreover, elevated AST/ALT levels not only reflect liver disease—a well-established risk factor for 30-day [42], 90-day [43], and 1-year mortality in CAP patients [44]—but are also positively correlated with long-term CVD mortality, as previously discussed. This underscores the need for clinicians to closely manage existing liver and heart conditions, while continuously monitoring relevant symptoms, physical signs, laboratory findings, and imaging results. Proactive management may help prevent deterioration or exacerbation of these conditions, potentially leading to better short- and long-term outcomes for CAP patients, especially those with T2DM.

Our study has several limitations worth noting. Firstly, the primary outcome of our study was defined as treatment outcome, which was infrequently used in previous studies, thus limiting the comparability of our results. Further analysis of AST/ALT in CAP patients is therefore underway to evaluate its value. Secondly, due to insufficient data, we were unable to explore the impact of treatment on laboratory parameters included in this study. Thirdly, the elevation of AST/ALT ratio may be induced by alcohol consumption, liver or heart abnormalities [45]. Patients with alcohol drinking or preexisting liver or heart-related disease were not excluded, and we recognize that this inclusion may potentially affected the results derived from this research. Fourth, this study does not account for patients' BMI, which is strongly associated with T2DM, or the presence of NAFLD, found in over 70% of T2DM patients. Both factors can significantly influence the AST/ALT ratio in our target cohort, and their exclusion may have affected our results. Future studies replicating this research should incorporate these variables for a more thorough analysis.

Conclusion

In summary, this study identified distinctive characteristics between hospitalized CAP patients with and without T2DM. Independent predictors of treatment outcomes in CAP patients with T2DM included CURB-65, PLR, AST/ALT, and WBC. Among these laboratory indices, AST/ALT demonstrated discriminative, predictive and prognostic value. When added to the CURB-65 score, AST/ALT resulted in improvement in terms of AUC, NRI, and IDI. Furthermore, a Fagan's nomogram is derived to enable a quick individual risk assessment. To gain a thorough understanding of the role of AST/ALT in CAP patients with T2DM, it might be worth taking NAFLD and CVD into account as well. Furthermore, AST/ALT was identified as a significant risk factor for all CAP patients included in this study, regardless of their diabetes conditions. Additionally, combining it with CURB-65 also improved the performance of the original scoring system for individuals in this population.

Abbreviations

CAP	Community-acquired pneumonia
T2DM	Type 2 diabetes mellitus
PSM	Propensity score matching
AUC	Area under the receiver operating characteristic curve
AST/ALT	Aspartate aminotransferase/alanine aminotransferase ratio
PLR	Platelet-lymphocyte ratio
OR	Odds ratio
CI	Confidence interval
IDI	Integrated discrimination improvement
COPD	Chronic obstructive pulmonary disease
PSI	Pneumonia Severity Index
WBC	White blood cell count
IQRs	Interquartile ranges
NRI	Net reclassification improvement
NEU	Neutrophil
LYM	Lymphocyte
PLR	Platelet-lymphocyte ratio
NLR	Neutrophil-lymphocyte ratio
GLU	Glucose
HbA1c	Glycated hemoglobin A1c
APTT	Activated partial thromboplastin time
K	Potassium

AST	Aspartate aminotransferase
5′-NT	5′-Nucleotidase
ADA	Adenosine deaminase
ALP	Alkaline phosphatase
CHE	Acetylcholine esterase
GGT	γ-Glutamyltransferase
CK	Creatine kinase
LOS	Length of stay
ROC	Receiver-operating characteristic
NAFLD	Nonalcoholic fatty liver disease
CVD	Cardiovascular disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03488-1.

Supplementary Material 1.

Acknowledgements
Not applicable.

Clinical trial number
Not applicable. And the study was not registered.

Authors' contributions
HZ and SL conceptualized the research. HZ, XZ, YZ, and WX collected the data. HZ and XZ analyzed the data, HZ, YZ, and WX drafted the manuscript. SL supervised the research and edited the manuscript. All authors read and approved the final manuscript.

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

Declarations

Ethics approval and consent to participate
Ethics approval for this study was obtained from the Ethics Committee of The People's Hospital of Nanchuan, Chongqing (YXYJ-2021–016-01). As data were retrieved from existing medical records, the requirement for informed written consent from individual participants was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Endocrinology, People's Hospital of Nanchuan, Chongqing 408400, People's Republic of China. [2]Department of Respiratory and Critical Care Medicine, People's Hospital of Nanchuan, Chongqing 408400, People's Republic of China. [3]Department of Public Health, People's Hospital of Nanchuan, Chongqing 408400, People's Republic of China.

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