

# Admission biochemical test associated with the prognosis of COVID-19: a multi-centered retrospective cohort study

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# Abstract

**Objectives:** Since December 2019, an outbreak of Corona Virus Disease-2019 (COVID-19) started in Wuhan, China. Now we comprehended much more about the troublesome disease from studies than the beginning. But more details between admission laboratory test and prognosis of COVID-19 were still confusing. So we focused on the admission biochemical test, and tried to verify their influence to the prognosis of COVID-19.

**Method:** 522 patients from 4 hospitals were enrolled in this retrospective cohort study. We collected demographic information, comorbidities and laboratory biochemical indicators, then compared them between survivors' and nonsurvivors' group. Logistic regression methods were used to explore the risk factors associated with in-hospital death. Linear regression and receiver operating characteristic curve (ROC-curve) was applied to assess the efficiency of risk factors and regression model.

**Results:** Age of nonsurvivors' group (68.9) was older than survivors group (50.0). Diabetes (68.7%) was the most common comorbidity in the nonsurvivors' group. In univariate regression analysis, most biochemical tests were related to the mortality except lipid metabolic results. Age, fasting blood glucose and blood urea nitrogen (BUN) were with a p-value less than 0.001 in multivariate regression model.

**Conclusion:** Age, BUN and fasting blood glucose were risk factors associated with the prognosis of COVID-19 related pneumonia.

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## Introduction

Since December 2019, COVID-19 outbreak and started to spread in Wuhan, China. The virus was confirmed and isolated in January 7, 2020 [1,2]. Compared to early stage of disease occurred, now we know much more clinical information and other knowledge about COVID-19. Some descriptive studies had showed us the main characters and risk factors for patients and disease progression [3-6], and some of the results were related about metabolic comorbidities and organ function. Recently, sequential organ failure assessment (SOFA) score and D-dimmer were proved to had bad effect on mortality.

Organ dysfunction, such as acute kidney failure and cardiac failure, were common findings in nonsurvivors' group [7]. A meta analysis about COVID-19 also reminded us that patients with previous cardiovascular metabolic comorbidities might face a greater risk of developing into the severe condition and in-hospital death [8]. All the researches mentioned above gave us an impression that organ function and metabolic status may be related to the mortality of COVID-19. Biochemical test was usually applied to assess the organ function and metabolic status directly. But more details about laboratory test of COVID-19 were still unclear. So we designed the retrospective cohort analysis to explore whether the admission biochemical test affected the prognosis of COVID-19.

## Subjects And Method

Subjects: Data of 522 patients were collected from 4 designated hospitals of COVID-19 treatment (Hubei Provincial Hospital of Traditional Chinese Medicine, Jin Yin-tan Hospital, Renmin Hospital of Wuhan University, Hubei Provincial Hospital of Integrated Chinese & Western Medicine). All adult patients who were diagnosed with COVID-19 according to WHO interim guidance were screened, and those who died or were discharged between Jan 2, 2020 (ie, when the first patients were admitted) and Feb 15, 2020, were included in our study.

Data collect: Real-time RT-PCR method was implemented for laboratory confirmation by local medical institution and local Centers for Disease Control and Prevention. Throat-swab specimens from upper respiratory were obtained as the medium of virus for Real-time RT-PCR. All patients received CT scan before or after admission and pneumonia was manifested. Data for laboratory test, outcome, demographic information and comorbidities of patients were taken from medical records. The demographic data included gender, age and prognosis. Comorbidities of diabetes mellitus, hypertension and coronary heart disease were obtained. Laboratory indicators of organ functions and metabolic status were tested with conventional test method within 24 hours of admission. Liver functions included alanine transaminase (ALT) and aspartate aminotransferase (AST). Kidney functions included creatinine (Cre), urea nitrogen (BUN). Myocardial functions included hypersensitive troponin T (hs-TnI), Brain natriuretic peptide (BNP). Fasting blood glucose, uric acid (UA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were also obtained for glucose, purine, and lipid metabolism evaluation.

Outcome events were in-hospital death or discharge. The criteria for discharge were normal body temperature for at least 3 days, substantial improvement in clinical respiratory symptoms and both lungs in chest CT, and two throat-swab samples negative for the virus test obtained at least 24 h apart.

Statistical analysis: Patients were divided into two groups by prognosis, survivors and nonsurvivors. Categorical variables was analysed by Chi-squared test method. Continuous variables were analyzed by independent sample t-test. All the continuous variables passed test of normality by shapiro-wilk method, with p-value < 0.01 as a criterion. Continuous variables were transformed into categorical variables (normal and abnormal), then univariate and multivariate logistic regression analysis were adopted for identifying risk factors of the prognosis. All variables from univariate analysis with  $P < 0.05$  were collected for the multivariate logistic regression analysis. Stepwise regression analysis was used to find the final risk factors related to the prognosis. Variables were removed step by step until p-values of all the left variables were less than 0.05. Kaplan-Meier method was used to make the survival curve of age, BUN and blood glucose. Risk factors, including age, blood glucose and BUN, were divided into different levels and the mortality was calculated in each levels. Linear regression model was used testing the mortality increase changed by the rising of risk factors. One patient with a hypoglycemia died after admission, the data was removed in the linear regression model of fasting blood glucose, for our purpose was to study

the mortality affected by hyperglycemia. Receiver operating characteristic curve(ROC curve) was used to evaluate the efficiency of the risk factors and regression model.

## Results

522 patients were enrolled in this cohort study. The range of age was between 18 to 92 years old, the median age was 54.2 years(IQR 43.0-68.9). Medium age of survivors was 50.0 years, while the nonsurvivors was 68.9. Nonsurvivors presented to be older than the survivors, and the result was statistically different( $p < 0.001$ )(table 1). 250 male(47.9%) and 272 female(52.1%) patients were analysed totally. Male patients in nonsurvivors' group(59.1%) accounted for a higher proportion than in survivors' group(44.7%)(Table 1). Comorbidities were more common in nonsurvivors' groups.Hypertension(24.9%) was the most common comorbidity in all patients, then followed by diabetes(18.0%) and coronary heart disease(7.2%). But in nonsurvivors' group, the odds for diatbetes(68.7%) were the highest, then followed by hypertension(40.9%) and coronary heart disease(13.0%)(Table 1).

Table 1.demographic information and comorbidities

Variables	Total (n=522)	Survivors (n=407)	Nonsurvivors (n=115)	P-value
Gender(male)	250(47.9%)	182(44.7%)	68(59.1%)	0.009
(female)	272(52.1%)	225(55.3%)	47(40.8%)	
Age	54.2(43.0,66.0)	50.0(40.0, 60.0)	68.9(62.0,76.5)	<0.001
Diabetes(yes)	94(18.0%)	16(3.9%)	79(68.7%)	0.015
Hypertension(yes)	130(24.9%)	83(20.4%)	47(40.9%)	<0.001
Coronary heart disease(yes)	38(7.2%)	23(5.7%)	15(13.0%)	0.013
ALT(U/L)	37.7(16.0-44.0)	35.5(16.0-40.0)	45.3(16.0-54.0)	0.07
AST(U/L)	35.9(19.0-42.0)	30.4(18.0-36.0)	55.1(27-61)	<0.001
Cre(umol/L)	73.3(52.9-79.2)	66.5(52.0-73.1)	98.3(57.4-102.3)	<0.001
BUN(mmol/L)	5.61(3.50-6.30)	4.65(3.30-5.53)	9.11(4.90-10.37)	<0.001
BNP(pg/ml)	187.9 (30.5-183.8)	175.5 (23-143.3)	221.6 (48.0-242.7)	0.29
hsTnI(ng/ml)	0.079 (0.002-00.020)	0.042 (0.001-0.008)	0.172 (0.007-0.040)	0.024
Blood glucose(mmol/L)	6.88(4.99-7.4)	6.32(4.89-6.70)	8.94(5.93-10.05)	<0.001
TC(mmol/L)	3.92(3.36-4.41)	3.96(3.40-4.48)	3.73(3.17-4.25)	0.026
TG(mmol/L)	1.51(1.01-1.71)	1.51(0.99-1.72)	1.52(1.11-1.62)	0.860
HDL(mmol/L)	1.03(0.84-1.16)	1.05(0.85-1.17)	0.96(0.76-1.13)	0.009
LDL(mmol/L)	2.19(1.74-2.62)	2.25(1.81-2.68)	1.99(1.62-2.31)	<0.001
UA(umol/L)	245.3 (186.4-305.0)	256.5 (197.7-315.7)	232.8 (153.0-285.0)	0.021

Data were shown as mean(Q1, Q3), or n(%). P value was less than 0.001 was recorded as p<0.001, otherwise actual p value was presented. ALT: alanine transaminase; AST: aspartate aminotransferase; Cre: creatinine; BUN: blood urea nitrogen; hs-TnT: hypersensitive troponinT; BNP: Brain natriuretic peptide; UA: uric acid; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

In organ function and metabolic status evaluation, liver function(ALT, AST) rose up mildly in nonsurvivals' group. Cre and BUN, the biochemical indicators of renal function, also products of protein metabolism, elevated obviously. Cardiac function contained BNP and hsTnI, hsTnI presented a meaningful elevation as a biomark for myocardium injury. On the contrast, BNP, often used to reflect the pressure of heart, atrium especially, showed no difference between survivors and nonsurvivors(Table 1). Fasting blood glucose obviously raised up in nonsurvivors' group(survivors 6.32 vs. Nonsurvivors 8.94), the results of lipid(TC, HDL, LDL) and nucleic acid metabolism(UA) declined(Table 1).

In the univariated logistic analysis, most comorbidities and abnormalitie of biochemical result indicated a bad clinical outcome, except BNP and lipid related results(Table 2). Variables with p-values < 0.05 stepped into multivariable logistic analysis, using stepwise regression method. Finally age, blood glucose and BUN were statistically proved to be closely related with the in-hospital mortality of COVID-19(Table 2). Kaplan-Meier method was used to made the survival curve of age, BUN and fasting blood sugar. All the p-values of the survival analysis were less than 0.001(Figure 1). In linear regression model test, close correlations were established between the mortality and risk factors, especially beyond physiological range(Figure 2). ROC curve were observed to test the logistic regression model. For the single variables, age seemed to get the best sensitivity(60.500[0.752,0.800], AUC:0.843), and BUN get the best specificity(6.695[0.884,0.575], AUC:0.792). In multivariables regression model, sensitivity and AUC increased (74.750[0.786,0.832], AUC:0.890)(Figure 3).

Table 2 .logistic regression analysis

Univariate analysis			Multivariate analysis			
Variables	OR	95%CI	P-value	OR	95%CI	P-value
Gender(male vs. female)	1.79	1.18-2.72	0.006			
Diabetes(yes vs. no)	1.89	1.15-3.10	0.014			
Hypertension(yes vs. no)	2.68	1.72-4.18	<0.001			
Coronary heart disease (yes vs. no)	2.49	1.25-4.95	0.012			
Age( $\geq$ 60 yeas vs. <60)	12.12	7.28-20.17	0.001	10.45	5.58-19.58	<0.001
ALT( $\geq$ 50 yeas vs. <50)	1.78	1.1-2.88	0.02			
AST( $\geq$ 40 yeas vs. <40)	5.35	3.4-8.4	<0.001			
Cre( $\geq$ 111 yeas vs. <111)	10.08	4.75-21.4	<0.001			
BUN( $\geq$ 9.5yeas vs. <9.5)	23.35	10.4-52.44	<0.001	11.77	4.32-32.07	<0.001
BNP( $\geq$ 520 yeas vs. <520)	0.66	0.73-3.76	0.223			
hsTnI( $\geq$ 0.06 yeas vs. <0.06)	8.28	3.31-20.71	<0.001			
Blood glucose( $\geq$ 6.1 yeas vs. <6.1)	4.39	2.67-7.2	<0.001	1.91	1.07-3.43	0.028
TC( $\geq$ 5.2yeas vs. <5.2)	0.88	0.32-2.41	0.805			
TG( $\geq$ 1.7yeas vs. <1.7)	0.94	0.55-1.61	0.812			
HDL( $\geq$ 1.16 yeas vs. <1.16)	0.65	0.36-1.16	0.131			
	0.79	0.22-2.8	0.717			

LDL( $\geq 3.4$ yeas vs. $< 3.4$ )		3				
UA( $\geq 300$ yeas vs. $< 300$ )	0.55	0.33-0.9 2	0.018			

P value was less than 0.001 was recorded as  $p < 0.001$ , otherwise actual p value was presented. OR: Odds Ratio; CI: Confidence interval; P value was less than 0.001 was recorded as  $p < 0.001$ , otherwise actual p value was presented. ALT: alanine transaminase; AST: aspartate aminotransferase; Cre: creatinine; BUN: blood urea nitrogen; hs-TnT: hypersensitive troponinT; BNP: Brain natriuretic peptide; UA: uric acid; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

## Discussion

This study finally identified several risk factors from variables about demographic data, comorbidities and biochemical analysis of organ functions and metabolic status.

From the researches mentioned above, male patients were more susceptible to COVID-19[6,7]. In our study, there was no obviously susceptibility enhancement in male group of the whole patients, but there was an upward trend of male patients in non-survivors' group. Patients with more severity would be prior to be admitted, so male patients might be in the majority in some early studies while the medical sources were limited.

Age was proved to be an important risk factor[7], that was also confirmed in our study. In our data collected, mortality increased rapidly while the patients were over 60 years old. (Table S1). Elderly individuals are physically frail and are likely to have several comorbidities, which not only increase the pneumonia susceptibility[9], but also affect their prognosis[10]. It had been proved in SARS and MERS[11,12]. In COVID-19, lymphopenia was common in blood test. And the function of lymphocyte would decrease accompanied by aging process, that would exacerbate losing control of viral replication and increasing the proinflammatory responses, potentially aggravating the disease progression and in-hospital death[13]. And in our study, in-hospital death was rare in the group of people younger than 40 years old, that reminded us a large group of asymptomatic carriers of young people might exist.

Diabetes had been reported to be closely related to regression and mortality of COVID-19[6,7], it was also proved in our univariate regression analysis (Table 2). But fasting blood glucose was not explained in the studies mentioned above. In our study, fasting blood glucose was confirmed to be higher in non-survivors' group. One possibility causing hyperglycemia was diabetes, another one was a stress-related hyperglycemia which caused by emergencies. Glycated hemoglobin might help us identify the different mechanism, but we didn't take it as a routine test on admission, so no result about glycated hemoglobin could be presented. In some other respiratory epidemic diseases, such as influenza, diabetes was an important risk factor closely related to mortality[14,15]. It is partially because 90% type 2 diabetes

accompanied with obesity, which was a risk factors to respiratory disease[16], and also because of damaged immunological functions caused by chronic hyperglycemia[17,18]. In our study, we ensured the fasting blood glucose was a risk factor to in-hospital death, and mortality increased obviously while the fasting blood glucose was beyond the upper level of normal range(6mmol/L)(Table S2). We emphasized an acute stress hyperglycemia also contributed to mortality besides the chronic glucose metabolic disorder. Stress hyperglycemia was a physically reaction to diseases, rather than psychological, and usually caused by catecholamines, hypothalamic pituitary adrenal(HPA) axis activation, inflammatory cytokines and lipotoxicity[19]. In virus infection, the rate of glucose uptake by infected cells increased continually, and the subsequently enhanced glycolysis results in higher glucose consumption and extracellular concentration of lactate[20,21]. In fact, hyperglycemia is a common finding in patients in hospital and indicates poor clinical outcome and mortality[22]. Hyperglycemia without diagnosed diabetes would be inclined to happened to the patients who got pancreatic reserve deficiency and insulin resistance[19], especially those who unaware of their status[23]. Patients with newly diagnosed hyperglycemia had a significantly higher mortality rate and a lower functional outcome than patients with a known history of diabetes or normoglycemia[21]. In ICU ward, patients who needed treatment for hyperglycaemia those without diabetes had higher SOFA scores, greater hospital length of stay, and higher mortality rates than the patients with known diabetes, despite lower median glucose and adjustment for severity of illness and other covariates[24].

BUN and Cre could elevated for acute kidney injury(AKI) in patients without chronic kidney failure. In our research, means of BUN and Cre rose up in nonsurvivors' group. Means of the two indicators in both survivors' and nonsurvivors' group were both in a relatively normal range of BUN and Cre, but there was still almost 50% percent increasement in nonsurvivors' group in average. According to Acute Kidney Injury Network( AKIN) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease(RIFLE) criterions for AKI, 50% rise of Cre can predict risk factors of acut kidney failure[25,26]. From the researches mentioned above, acute kidney injury would appear in about 50% patients in nonsurvivors' group compared to 1% in survivors', but that pathological course ususlly happened 16 days after the disease was onset, or 4 days after ICU admission[7]. So the baseline elevation of BUN and Cre should be hints for early stage of kidney damage and contributed to bad mortality.

In COVID-19, the elevation of fasting blood sugar and BUN maybe indicated more information. Lymphopenia was normal and distinct clincal character of cov-19 infected disease. In virus infected model, T cells would upregulate the uptake and utilization rates of glucose and amino acids promoting anabolic growth while stumulated by infection[27], so anabolism decrease caused by lymphopenia might aggravate the rise of BUN and blood sugar under a exacerbation of catabolism. We can speculated high level of BUN and blood-glucose might reflect quantitative or functional damage of T cell that would increase the glucogenesis and amino acid anabolic.

Results about and lipid metabolism seemed change little during early stage of this disease. So disorders about purine and lipid metabolism might need more researches.

AST was removed in the last step of multivariable regression analysis, but it still aroused out interest. AST showed a obvious difference( $p < 0.001$ ) between two groups, while the ALT didn't( $p = 0.07$ ). Abnormalities of liver function was still under discussion in the clinical course of COVID-19[28,29]. And besides liver function, AST was also used to evaluate myocardium damage. Some reports indicated that higher visit-to-visit variability of liver enzymes was an independent predictor of all-cause mortality and cardiovascular events[30,31]. From the analysis mentioned above, acute cardiac injury would appear in about 59% patients in nonsurvivors' group compared to 1% in survivors', and usually happened 15 days after admission with acute elevation of hsTnI[7]. So elevation of AST might be a hint of myocardium damage at the early stage besides liver dysfunction in COVID.

Since the incubation period and most patients would have to spent several days waiting the confirmative diagnosis for admission, the biochemical test on admission reflected the body reaction to COVID-19. Lots of supplements were needed in our study. Glycated hemoglobin would be good for classifying the reason of hyperglycemia besides history of diabetes. Dynamic changes of renal and cardiac function should be observed to assess the efficiency of alarms from biochemical test on admission.

## Declarations

### Acknowledgements

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### Ethics approval and consent to participate

The Institutional Ethics Committees of Hubei Provincial Hospital of Traditional Chinese Medicine approved this retrospective study(HBZY2020-C14-01). Due to the speed of COVID-19 spread and the risk of infection, exemption from the written informed consent was obtained. The original data was not shared publicly for the specificity of the disease at present.

### Author contribution

Gang Li and Qi Long were contributed to statistical method design and meta analysis, main part of the article was finished by Qi Long. Ye-ming Wang, Bin Song and Chen-liang Zhou were contributed to data collected, Qiu-fen Dong, Xiao-bin Cheng and Liu-lin Wang were contributed to data input and arrangement. All authors reviewed the manuscript.

### Competing interests

The authors declare no competing interests.

## Statement

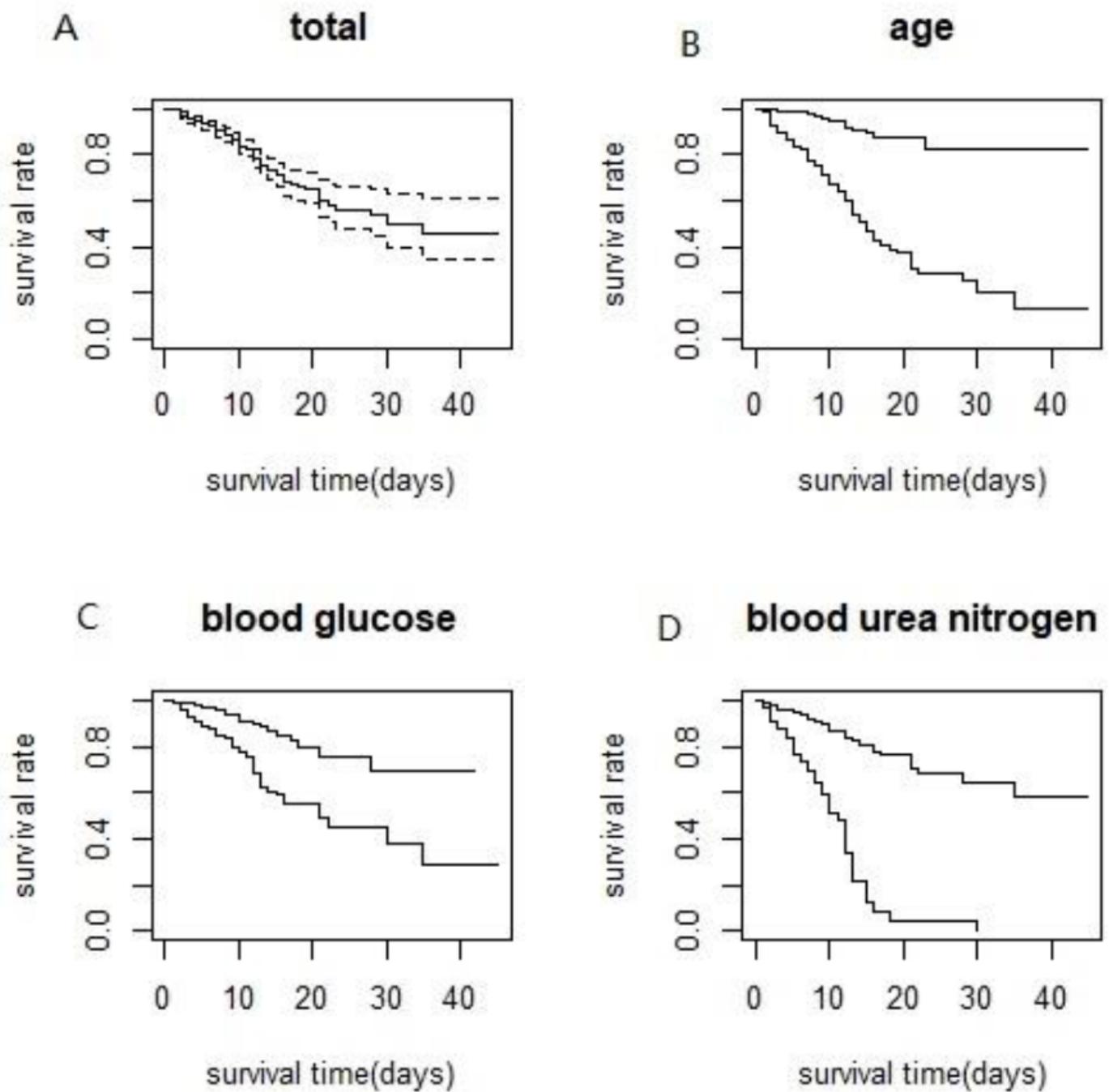
Patients included in this retrospective analysis have not been reported in any other submission by ourselves or anyone else.

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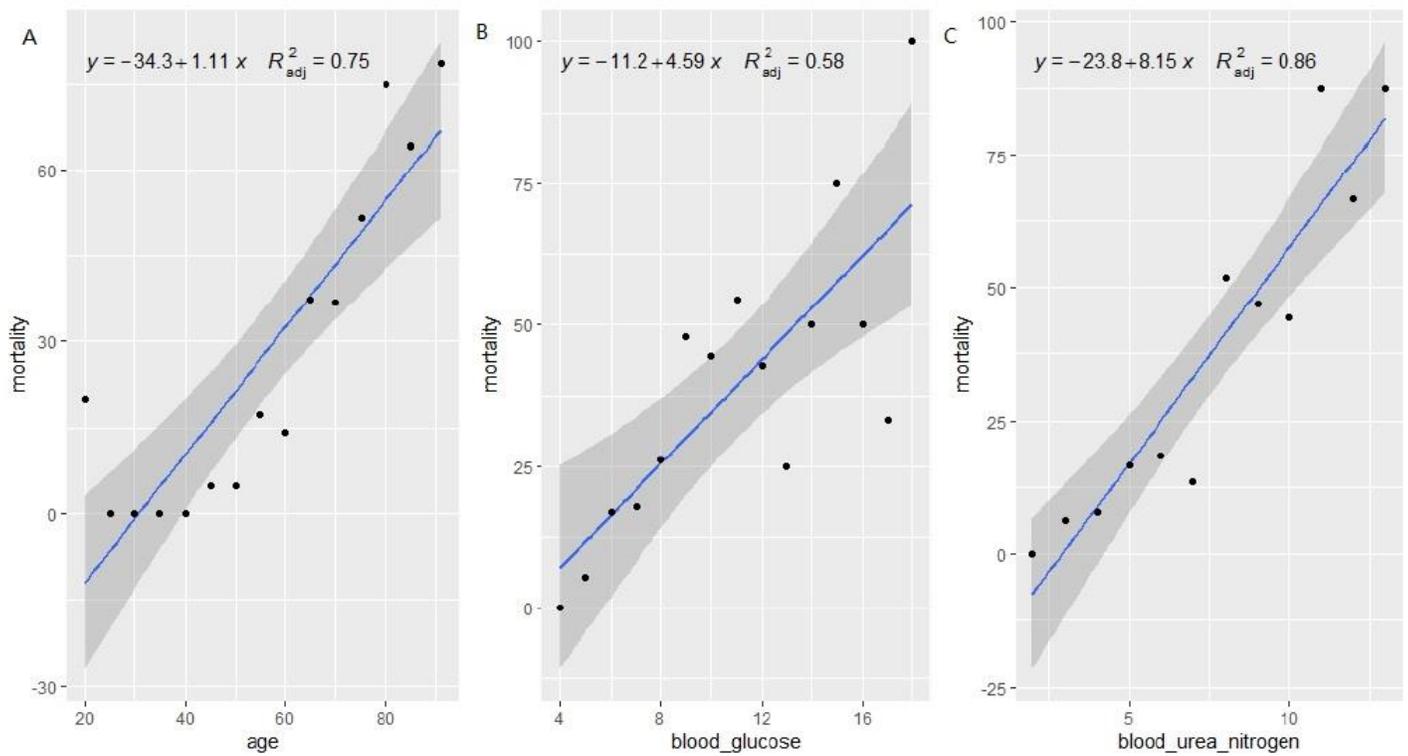
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## Figures



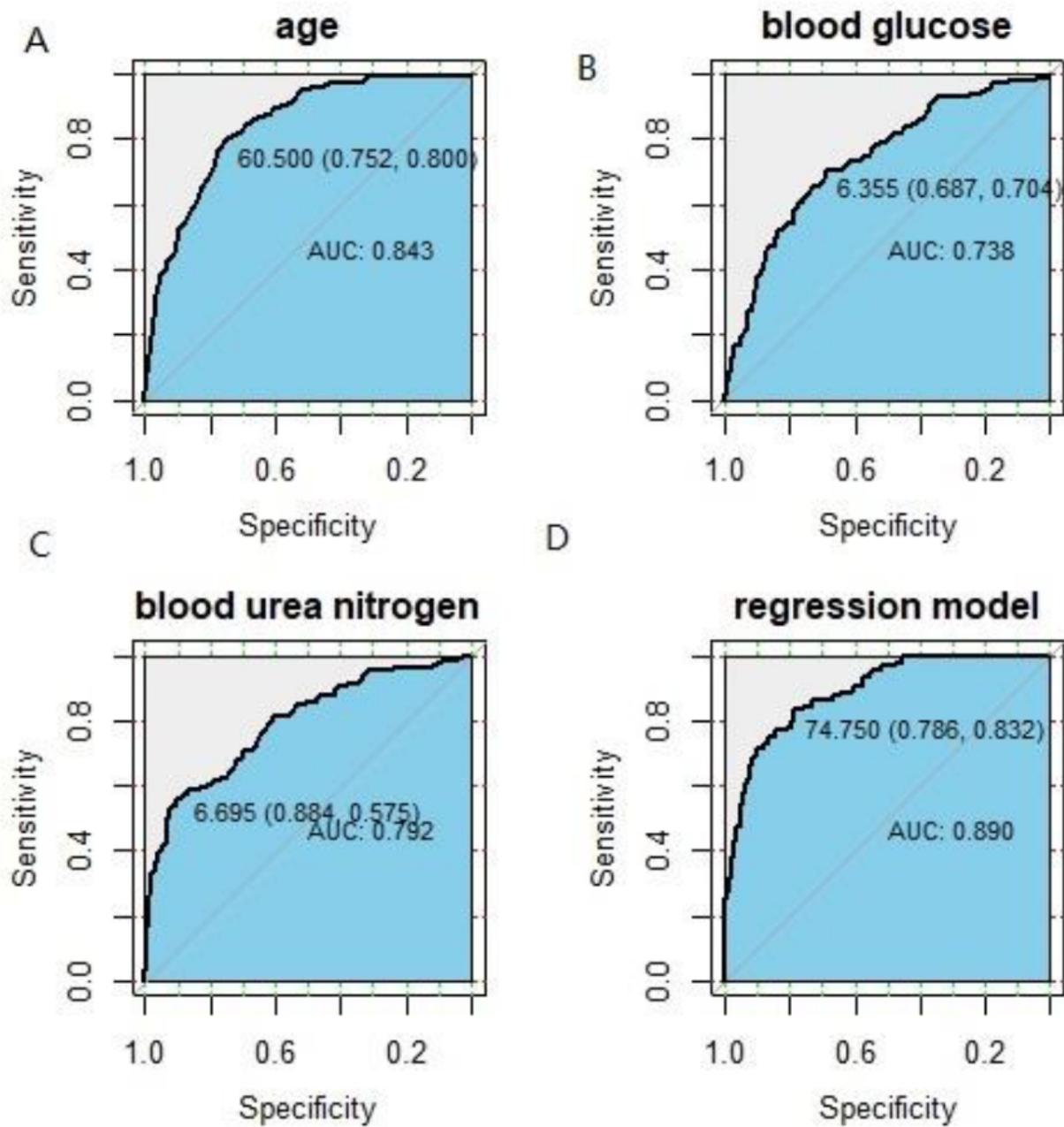
**Figure 1**

Kaplan-Meier survival analysis for risk factors. (A) Survival curve for the overall mortality; (B) Survival curve for age,  $p < 0.001$ ; (C) Survival curve for blood glucose,  $p < 0.001$ ; (D) Survival curve for blood urea nitrogen,  $p < 0.001$ .



**Figure 2**

Linear regression models for correlations between risk factors and mortality increase. (A) Linear regression model for age; (B) Linear regression model for blood glucose; (C) Linear regression model for blood urea nitrogen.



**Figure 3**

Receiver operating characteristic(ROC) curvefor risk factors. (A)ROC curve for age; (B)ROC curve for blood glucose; (C)ROC curve for blood urea nitrogen; (D) ROC curve for the regression models formed by age, blood glucose and blood urea nitrogen.

## Supplementary Files

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