Title Page

Title: Risk factors analysis and nomogram construction of non-survivors in critical patients with COVID-19

Running title: A nomogram of COVID-19

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Summary

A pandemic named coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbroke in China since December 2019. This disease has caused more than 70000 deaths worldwide. We intend to analyze the risk factors of death and establish a prognosis nomogram for critical patients with COVID-19. We analyzed the clinical data of COVID-19 patients in Zhongnan Hospital of Wuhan University who were critical cases with COVID-19 before March 20, 2020. Data were collected at admission and compared between survivors and non-survivors and analyzed by univariable and multivariable logistic regression analysis. Finally, 104 patients were included, and 50 of whom died. Age [OR 5.73 (95% CI, 1.14-28.81)], chest tightness [OR 5.50 (95%CI, 1.02-29.64)], AST [OR 6.57 (95%CI, 1.33-32.48)]and BUN [5.59 (95%CI, 1.05-29.74)] at admission were considered to predict the risk of death in critical patients and were selected to construct the nomogram. Subsequently, we established a nomogram model and validated it. The sensitivity and specificity of the nomogram were 96.0% and 74.1%, respectively. The AUC was 0.893 (95% CI, 0.807-0.980).

Introduction

At the end of 2019, a massive outbreak known as Corona Virus Disease 2019(COVID-19) emerged in Wuhan, China. Up to now, more than 200,000 cases have been confirmed around the world. The current COVID-19 outbreak is both similar and different to the prior Severe Acute Respiratory Syndromes (SARS) and Middle East respiratory syndrome (MERS). All three diseases initiated by zoonotic transmission of coronavirus which frequently lead to lower respiratory tract infection but different case-fatality rate (CFR). SARS was reported for an

overall CFR of 9.6%, causing 774 deaths across 29 countries (1). There are still sporadic cases of MERS and has a CFR of 34.4% with 858 deaths across 27 countries (1, 2). According to the Chinese center for disease control and prevention (CDC), about 5% COVID-19 patients were critical, the CFR was 49% among critical cases, and 2.3% in total (2). In addition, no deaths were reported in mild or severe cases (2). Although the overall CFR of COVID-19 is lower than that of SARS and MERS, COVID-19 has led to more total deaths due to the large number of infection cases (2, 3). Therefore, it is very important to identify those patients with high risk of death due to the high CFR in critical patients. However, the risk factors of deaths in COVID-19 patients in this subgroup remain unclear.

It is reported that critical COVID-19 cases can be presented as Acute Respiratory Distress Syndrome (ARDS), myocardial injury, kidney injury and central nervous system impaired, etc. (4-7). Therefore, death can be caused by a variety of factors. This study investigated the risk factors of death in patients with COVID-19 in our hospital.

Materials and Methods

Study design and participants

We performed a retrospective study on laboratory-confirmed COVID-19 patients in Zhongnan Hospital of Wuhan University before March 20, 2020. The diagnosis was confirmed when a positive result of quantitative real-time reverse-transcriptase polymerase-chain-reaction (qRT-PCR) on nasal and pharyngeal swab samples. Briefly, the swabs were placed into a virus preservation solution and the respiratory sample RNA isolation kit (Zhongzhi, Wuhan, China) was used to extract total RNA. The qRT-PCR assay was performed using a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid detection kit (Shanghai bio-

germ Medical Technology Co Ltd). Positive test result was defined as the cycle threshold value (Ct-value) less than 37, Ct-value ≥ 40 was defined as a negative test, and the Ct-value of 37-39 was defined as a suspicious result that need to be retested. These diagnostic criteria were based on the recommendation by the National Institute for Viral Disease Control and Prevention (China) (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html).

According to the diagnosis and treatment plan of novel coronavirus pneumonia (trial version 7) issued by the Chinese Health Committee, critical cases should meet one of the following criteria: 1) respiratory failure occurs and mechanical ventilation is required; 2) shock; 3) complicated with other organ failure and require intensive care unit (ICU) care. We selected cases that met the above diagnostic criteria, and all selected cases were excluded when: 1) non-critically ill; 2) no chest CT imaging within three days from admission; 3) without complete clinical and laboratory data.

All included patients were divided into survivors and non-survivors. This study was approved by Institutional Ethics Commission of Zhongnan Hospital, and informed consent was waived (No. 2020015).

Data collection

Clinical characteristics, laboratory findings and chest CT images of all critical patients were obtained from electronic medical records. The clinical characteristics included age, gender, exposure history, duration from symptom onset to admission, smoking history, comorbidities (hypertension, diabetes, coronary heart disease, chronic kidney disease, malignancy and chronic obstructive pulmonary disease (COPD)), symptoms (fever, cough, chest tightness, fatigue, myalgia and digestive symptoms) and complications (shock, respiratory failure, acute

renal failure, infections caused by other virus or common pathogens). The laboratory findings included white blood cell (WBC) count, neutrophils count, lymphocyte count, platelet (PLT) count, prothrombin time (PT), activation of partial thromboplastin time (APTT), D-dimer (DD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine, C-reactive protein (CRP), creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and procalcitonin (PCT).

The chest CT characteristics were reviewed by two radiologists and decisions were reached by consensus. The chest CT findings included whether the lesion occurred bilaterally, whether it was pure ground glass opacity (GGO), whether it was diffuse and normal lung volume ratio. GGO is defined as increased lung parenchymal attenuation that did not obscure the underlying vascular architecture. Diffuse is defined as the involvement of GGO and other lesions in the lung around the bronchi. Normal lung volume ratio was measured by Intelligent Evaluation System for Novel Coronavirus Pneumonia (YITU Healthcare, China, Hangzhou). This system combined the convolutional neural network and thresholding methods for segmentation of left and right lungs and detection of patchy shadows and calculated the normal lung ratio. We defined the cutoff CT value of the normal lung tissue as lower than -700Hu.

Statistical analysis

Categorical variables were described as percentages (%). Mean, median and interquartile range (IQR) were used to describe continuous variables. All variables were subject to univariate logistic regression. When P value was less than 0.05, the variables were included in binary logistic regression. Forward Stepwise (Wald) model was used for stepwise logistic regression analysis. The binary logistic regression analysis was employed to conclude a multivariate

model to predict the risk of death among critical patients.

Prognostic nomogram model was used to present the odds ratio (OR) and β of each predictor and to evaluate the risk of death by using the result of the binary logistic regression. One hundred points were assigned to the most dangerous predictor with the highest β coefficient, and the other predictors were given corresponding points based on weight. During the internal validation of the nomogram, 500 bootstrap resamples were performed to assess its predictive accuracy.

Univariate analysis was based on IBM SPSS 21.0 software. Multivariate regression analysis and nomogram was performed by R software 3.4.3 with rms statistical packages.

Results

As of March 20, 601 cases of COVID-19 were discharged in our hospital. Among them, 104 patients met the critical case criteria and were included in this study (Fig. 1). Based on final survival status, 50 (48.1%) cases were non-survivors and 54 (51.9%) survived. In non-survival patients, the median duration from admission to death was 15.0 (9.5-19.5) days, and the median duration from admission to discharge of the survivals group was 20.0 (18.0-30.0) days. The critical case rate and CFR was 17.3% and 4.5%, respectively.

Clinical characteristics

Clinical characteristics were presented in Table 1. The median age of critical patients was 66.0 years (range: 55.3-74.0 years), and 40 (80%) patients were above 65 years old in non-survivor group, which was more than that in survivor group (16, 29.6%) (p=0.001). 24 (23.1%) patients were complicated by other virus infection, and 48 (46.2%) patients were complicated by other pathogens infection, such as acinetobacter baumannii, candida albicans, and legionella

pneumophila. Comparing survivor group and non-survivor, no statistical significance was found in gender, exposure history, duration from symptom onset to hospital admission, smoking history and comorbidities between survivors and non-survivors. Chest tightness was more common in non-survival patients ($p < 0.05$). For laboratory parameters presented in Table 2, higher median levels of D-dimer [46 (44.2%),P=0.03], AST [40 (80.0%), p<0.001], BUN [36 (34.6%), p=0.007], and PCT [46 (92.0%), p=0.008] were significantly higher in the non-survivor group than that in the survivor group.

Chest CT findings

Chest CT findings were also demonstrated in Table 1. Bilateral lesions were present in more than half of the patients (98, 94.2%), as well as diffuse lesions (80, 76.9%). Only 38 (36.5%) patients showed pure GGO lesions, others combined with consolidation or septal thickening. Normal lung volume ratio did not present statistically significant between two groups.

Selected variables for prognosis model

Age>65 (p<0.01), chest tightness (p=0.007), D-dimer>500ng/ml (p=0.03), AST>35U/L (p<0.001), BUN>7.6mmol/L (p=0.007), PCT≥0.05ng/ml (p=0.008) were screened by univariate analysis which were significantly related to risk of death among critical patients. Stepwise (Wald) model was adopted for logistic regression analysis. Age, chest tightness, AST and BUN were the final variables selected to establish the prognosis model (Table 3).

Establishment and validation of nomogram model

Nomogram included all statistically significant prognostic factors in the binary logistic regression model, including four variables (age, chest tightness, AST, BUN) were used to develop a prognosis nomogram model (Fig. 2). According to the different classification of each

feature, points are projected upward to get the score of each item. As results, AST (100 points) was the greatest predictor for risk of death in critical patients, followed by age, BUN and chest tightness. Total points are calculated by adding all the points, and the non-survival risk rate of patients can be calculated by projecting the total points downward. The higher the score, the worse the survival prognosis. For a critical patient, the non-survival risk can be predicted by matching his clinical and laboratory results with this nomogram model so as to improve the efficiency and accuracy of the prediction.

ROC curve (Fig. 3) was used to validate the nomogram model. The sensitivity and specificity of the nomogram was 96.0% and 74.1%, respectively. The area under curve (AUC) was 0.893 (95% confidence interval, 0.807-0.980).

Discussion

In this retrospective study, 104 critical COVID-19 patients from 601 patients were confirmed to be COVID-19. The critical case ratio of this cohort is 17.3%, and the CFR is 4.5%. Compared to the previously reported critical case ratio (5%) and CFR (2.3%) of COVID-19 (2), our results seems to be higher, may be due to the fact that our healthcare center is a grade IIIA hospital, which received more severe and critical cases. The reported critical case ratio of SARS and MERS was (20-30)% and (50-89)%, respectively, which were higher than that in our cases (8-15). It seems that SARS-CoV-2 has a relatively lower pathogenicity, therefore, a shorter hospital stay [18.5 (13.3-24.8)] of critical patients than that in MERS [41 (8-96)] and SARS [25.05 ± 12.09] (16, 17) could be observed in COVID-19 patients.

The OR of age above 65 years old in the non-survival group is 5.73, which suggests that advanced age is a risk factor of death in critical COVID-19 patients. Same results were found

in studies of SARS, MERS and previous studies of COVID-19 (18-20). In our study, gender is not a risk factor for death in critical patients, since most critical patients (80, 76.9%) are male. This is also consistent with previous studies that male patients were more susceptible to SARS-CoV-2 infection than female (21).

It had been reported that comorbidities such as diabetes, hypertension, cancer, kidney and chronic lung diseases might be risk factors of death in SARS, MERS and COVID-19 (20, 21). However, in our study, these comorbidities were not risk factors of death for critical COVID-19 patients. This may be due to the different inclusion criteria of the previous studies, which did not differentiate critical patients from severe patients.

The most common symptoms in our study are also fever and cough, same as the general population reported before (21, 22). Through univariate analysis, chest tightness is the only symptom that is screened as a possible risk factor and has not been taken seriously in previous related reports (OR, 95%CI; 5.50, 1.02-29.64). According to this, we speculate that chest tightness may be an important manifestation of hypoxia or myocardial injury, which may develop eventual ARDS or myocardial infarction leading to the final death, also remind us to pay more attention to this symptom in critical patients.

As for laboratory findings, elevated D-dimer, AST, BUN and PCT is statistically significant between two groups according to univariate analysis. By further multivariate logistic regression analysis with stepwise (Wald) method, AST (OR,95%CI; 6.57, 1.33-32.48) and BUN (OR, 95%CI; 5.59, 1.05-29.74) are screened into the final model. AST is one of the indicators for evaluating liver function (23), and BUN is one of the indicators to evaluate renal function (24). It had been reported that the human homologue of angiotensin-converting enzyme (ACE2)

which was verified as the receptor of SARS-CoV is expressed in both liver and kidney, especially in the kidney (25, 26). So, we hypothesize that the two elevated indicators suggest the damage of the SARS-CoV-2 to liver and kidney. The higher value of these two indicators, the more likely to lead to death. As for other indicators, we speculate that these indicators may be common characteristics of critical patients.

CT parameters, whether descriptive or accurately measured, have no value in risk prediction for non-survivor patients in this group. The reasons may be listed as follows: (1) the lesion range of critical patients is large and bilateral(94.2%) which explained no statistical difference, and this result is similar to a previous study involving 41 people, among which 13 were admitted to ICU and 6 died; (2) consolidation or consolidation combined with GGO lesions occur in most critical patients(63.5%) leading to no difference on sign of GGO. However, it should be taken seriously when patients are with large lesion range, mixed lesion density or lower normal lung volume ratio for its high mortality.

Because the clinical manifestations of COVID-19 are not specific and are similar to the symptoms of influenza and other bacterial pneumonia, it is important to distinguish among these diseases. According to the pathogen test findings of included patients, 24 patients were of virus infection including influenza a and b, and 48 patients were with other pathogen infection such as legionella pneumophila, yeast-like spores and so on. Although there is no significant difference between the two groups in infection with other pathogens, it could be suggested that some critical patients also had other infections. It should be taken seriously to identify whether the pathogen was SARS-CoV-2 and treatment should be adjusted if a patient is infected with other pathogens in the meantime.

Complications are also a concern. In our study, 48 people developed shock, 64 developed respiratory failure, and 26 developed acute renal failure. Out of all non-survivors, 46(92.0%) developed respiratory failure, 20(40.0%) develop acute renal failure and 40(80.0%) developed shock. The incidence of all complications was much higher in non-survivor group than in the survivor group. So, in our view, as far as possible to maintain the critical patients breathing, monitoring the patient's blood pressure and renal function is an important means to avoid the death of critical patients. In a previous study, it had been reported that SARS predominantly caused severe respiratory failure, with little other organ failure (27). But at the moment, SARS-CoV-2 will not only cause respiratory failure, multi-organ failure is possible, especially among critical patients.

Prognosis nomogram model composed of age≥65(OR, 95%CI; 5.73, 1.14-28.81), chest tightness(OR, 95%CI; 5.50, 1.02-29.64), elevated AST (OR, 95%CI; 6.57, 1.33-32.48) and BUN(OR, 95%CI; 5.59, 1.05-29.74) can easily and quickly assess the risk of death of critical patients in clinical practice. What's more, the parameters selected in the model are also common in clinical practice, which can be convenient in clinical promotion. ROC presents good sensitivity (96.0%) and specificity (76.1%) of the model, and AUC is 0.893(0.807-0.980) which show that the prediction model is effective.

Some limitations in this study should be noted. First, the sample size of our study was not large enough which may cause some bias. Second, parameter selection was chosen at the time of admission. Due to the differences in symptoms, the timepoint of admission may also have bias. Third, because most of the treatments were carried out orderly according to the treatment plan, we only referred to the previous examination and clinical parameters and did not conduct a

systematic study on the possible differences in the treatment. Although there is no specific drug, it was reported that invasive positive pressure ventilation will help to improve the clinical cure rate. Therefore, it is meaningful to use the nomogram model in this study to identify the risk of death of critical patients early. We also look forward to more large sample multivariate studies. In conclusion, we have rarely seen studies of predicting risk of death among critical patients with COVID-19 until now. We offer a prognosis nomogram model based on accessible clinical data and hope it can bring more convenience to physicians to predict the death risk of critical patients, so as to develop better treatment strategies and reduce mortality.

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Conflict of interest: None to declare.

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Figure legends

Figure 1. Study flow diagram. It showed the process of enrolling patients; COVID-19= Corona Virus Disease 2019.

Figure 2. Nomogram model for assessing the risk of death in critical patients. Total points are calculated by adding all the points, and the non-survival risk rate of patients can be calculated by projecting the total points downward. The higher the score, the higher probability of death; AST= Aspartate transaminase; BUN= Blood urea nitrogen.

Figure 3. ROC curve of nomogram. It was to validate the nomogram model. The sensitivity and specificity of the nomogram was 96.0% and 74.1%, respectively. The area under curve (AUC) was 0.893 (95% confidence interval, 0.807-0.980).

Table 1. Clinical manifestations and imaging results of critical patients with COVID-19

	All patients (n=104)	**Survivors (n=54)**	**Non-survivors (n=50)**	**P value**
Age-median (IQR)	66.0 (55.3-74.0)	62.0 (49.0-73.0)	71.5 (61.8-78.8)	0.064
≤65- No. (%)	48 (46.2)	38 (70.4)	10 (20.0)	**0.001**
> 65- No. (%)	56 (53.8)	16 (29.6)	40 (80.0)	
Gender-No. (%)				0.613
Female	24 (23.1)	14 (25.9)	10 (20.0)	
Male	80 (76.9)	40 (74.1)	40 (80.0)	
Exposure-No. (%)				0.131
Yes	22 (21.2)	16 (29.6)	6 (12.0)	
No	82 (78.8)	38 (70.4)	44 (88.0)	
Onset of symptom to admission-days, median (IQR)	6.5 (2.0-10.0)	6.0 (3.0-10.0)	6.5 (0.0-11.0)	0.772
Smoking history-No. (%)				
Non smoker	78 (75.0)	46 (85.2)	32 (64.0)	0.897
Past smokers	10 (9.6)	0 (0.0)	10 (20.0)	0.641

Current smokers	16 (15.4)	8 (14.8)	8 (16.0)	0.999
Comorbidities-No. (%)				
Hypertension	48 (46.2)	24 (44.4)	24 (48.0)	0.797
Diabetes	12 (11.5)	6 (11.1)	6 (12.0)	0.920
Coronary heart disease	18 (17.3)	8 (14.8)	10 (20.0)	0.623
Chronic kidney disease	6 (5.8)	2 (3.7)	4 (8.0)	0.517
Malignancy	12 (11.5)	6 (11.1)	6 (12.0)	0.920
COPD	6 (5.8)	2 (3.7)	4 (8.0)	0.517
Symptoms and signs-No. (%)				
Fever	92 (88.5)	46 (85.2)	46 (92.0)	0.449
Cough	62 (59.6)	36 (66.7)	26 (52.0)	0.284
Chest tightness	54 (51.9)	18 (33.3)	36 (72.0)	**0.007**
Fatigue	58 (55.8)	24 (44.4)	34 (68.0)	0.091
Myalgia	16 (15.4)	10 (18.5)	6 (12.0)	0.518
Digestive symptoms	26 (25.0)	12 (22.2)	14 (28.0)	0.631
Complications-No. (%)				
Shock	48 (46.2)	8 (14.8)	40 (80.0)	**<0.001**
Respiratory failure	64 (61.5)	20 (37.0)	44 (88.0)	**0.001**
Acute renal failure	26 (25.0)	6 (11.1)	20 (40.0)	0.023
Virus infection	24 (23.1)	12 (22.2)	12 (24.0)	0.879

Other pathogen infection	48 (46.2)	26 (48.1)	22 (44.0)	0.764
Chest CT findings-No. (%)				
Bilateral	98 (94.2)	48 (88.9)	50 (100.0)	0.990
GGO	38 (36.5)	24 (44.4)	14 (28.0)	0.222
Diffuse	80 (76.9)	36 (66.7)	44 (88.0)	0.079
Normal lung volume ratio-mean($\bar{x}$ ±SD), %	65.8±20.8	70.0±19.5	61.2±21.5	0.132

IQR=Interquartile range; COPD=Chronic obstructive pulmonary disease; GGO=Ground glass shadow.

Table 2. Laboratory results of critical patients with COVID-19

WBC ($\times 10^9$/L; normal range 3.5-9.5)	6.61 (3.74-9.27)	6.13 (2.96-8.53)	6.76 (3.96-10.59)	0.465
Increased-No. (%)	26 (25.0)	12 (22.2)	14 (28.0)	0.906
Decreased-No. (%)	24 (23.1)	16 (29.6)	8 (16.0)	0.306
Neutrophils ($\times 10^9$/L; normal range 1.8-6.3)	4.65 (2.62-7.58)	3.75 (1.87-7.46)	5.50 (3.31-8.07)	0.389
Increased-No. (%)	32 (30.8)	16 (29.6)	16 (32.0)	0.739
Decreased-No. (%)	14 (13.5)	12 (22.2)	2 (4.0)	0.132
Platelet ($\times 10^9$/L; normal range 125-350)	142.0 (105.5-197.0)	162.0 (115.0-201.0)	125.0 (96.5-190.5)	0.767
Decreased-No. (%)	42 (40.4)	18 (33.3)	24 (48.0)	0.284
PT, (s; normal range 9.4-12.5)	13.2 (12.4-14.6)	13.1 (12.4-14.4)	13.5 (12.0-15.4)	0.293
Increased-No. (%)	72 (69.2)	38 (70.4)	34 (68.0)	0.853
APTT, (s; normal range 25.1-36.5s)	30.6 (28.3-34.8)	30.0 (28.0-32.0)	33.8 (28.8-36.5)	0.163
Increased-No. (%)	14 (13.5)	2 (3.7)	12 (24.0)	0.060
D-dimer, (ng/ml; normal range 0-500)	387.5 (224.8-1186.5)	263.0 (169.0-900.0)	764.0 (318.5-2042.5)	0.253
Increased-No. (%)	46 (44.2)	16 (29.6)	30 (60.0)	**0.030**
ALT, (U/L; normal	34.0 (22.0-	32.0 (21.0-	38.0 (25.5-	0.895

range 7-45)	51.8)	52.0)	50.5)	
Increased-No. (%)	34 (32.7)	18 (33.3)	16 (32.0)	0.918
AST, (U/L; normal range 13-35)	46.0 (26.3-76.3)	29.0 (25.0-69.0)	54.0 (42.0-102.0)	0.182
Increased-No. (%)	54 (51.9)	14 (25.9)	40 (80.0)	**<0.001**
BUN, (mmol/L; normal range 2.8-7.6)	7.8 (5.0-12.5)	10.8 (5.7-17.0)	6.0 (4.7-8.3)	**0.041**
Increased-No. (%)	54 (51.9)	18 (33.3)	36 (34.6)	**0.007**
Creatinine, (μmol/L; normal range 49-90)	84.2 (66.7-107.1)	75.1 (62.6-91.0)	88.4 (71.6-121.2)	0.503
Increased-No. (%)	40 (38.5)	16 (29.6)	24 (48.0)	0.177
CRP, (mg/L; normal range 0-10)	61.6 (31.8-125.7)	37.6 (18.1-76.8)	102.9 (50.3-159.7)	**0.006**
Increased-No. (%)	96 (92.3)	48 (88.9)	48 (96.0)	0.356
CK, (U/L; normal range<145)	143.0 (78.3-240.8)	119.0 (62.0-226.0)	193.0 (84.5-378.5)	0.460
Increased-No. (%)	50 (48.1)	20 (37.0)	30 (60.0)	0.101
CKMB, (U/L; normal range 0-25)	23.0 (12.3-42.8)	18.0 (11.0-42.0)	28.0 (14.0-44.0)	0.327
Increased-No. (%)	48 (46.2)	18 (33.3)	30 (60.0)	0.057
PCT, (ng/ml; normal range<0.05)	0.13 (0.01-0.69)	0.07 (0.00-0.39)	0.43 (0.10-1.39)	0.227

Increased-No. (%)	76 (73.1)	30 (55.6)	46 (92.0)	**0.008**

WBC=White blood cell; PT=Prothrombin time; APTT=Activated partial thromboplastin time; ALT=Alanine transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; CRP=C-reactive protein; CK=Creatine kinase; CKMB= Creatine kinase MB; PCT=Procalcitonin.

Table 3. Death risk factor of critical COVID-19 patients.

Variable	Survivors (n, %)	Non-survivors (n, %)	OR (95% CI)	P value
Age>65	16 (29.6)	40 (80.0)	5.73 (1.14-28.81)	0.034
Chest tightness	18 (33.3)	36 (72.0)	5.50 (1.02-29.64)	0.047
AST>35U/L	14 (25.9)	40 (80.0)	6.57 (1.33-32.48)	0.021
BUN>7.6 mmol/L	18 (33.3)	36 (34.6)	5.59 (1.05-29.74)	0.044

OR=Odds ratio; AST= Aspartate transaminase; BUN= Blood urea nitrogen.

Fig.1 Study flow diagram.