Early prediction for severe COVID-19 with hypertension and intervention

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Research article

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Abstract

Background

To identify the early predictors of severe coronavirus disease 2019 (COVID-19) with hypertension,explore antihypertensive drugs with potential therapeutic effects, and provide a basis for clinical prediction and treatment decisions.

Method:

A retrospective study was performed on all included cases.

Results

A total of 68 COVID-19 patients with hypertension were included,27 (39.7%) was severe and 41 (60.3%) was non-severe. Between the non-severe group (n = 41) and the severe group (n = 27),number of elevated B-type natriuretic peptide (BNP) and abnormal renal function,and albumin,lactate dehydrogenase,ultrasensitive troponin I,PH Value,arterial carbon dioxide partial pressure,sodium,osmotic pressure (OP),blood sugar (BS) and oxygenation index (OI) are significantly different.While age, male gender,comorbidities with diabetes or atherosclerotic cardiovascular disease,smoking history,number of abnormal liver function,heart rate,respiratory rate, blood pressure,white blood cell count,hematocrit,potassium and lactic acid are statistically insignificant.Four independent predictors of BNP (P = .026),OP (P = .004),BS (P = .017) and OI (P = .001) are obtained through multivariate binary logistic regression model.The area under curve (AUC) of receiver operating characteristic (ROC) of model is 0.904 ([95%CI] [0.832–0.976];P = .000),with excellent performance.Compared with blank control group (n = 27) and other antihypertensive drugs group (n = 20),OP ([287.3 ± 5.7] vs [283.5 ± 6.1];P = .045) ([287.3 ± 5.7] vs [281.9 ± 5.4];P = .007) in renin-angiotensin-aldosterone system (RAS) inhibitors group (n = 21) have increased significantly.Compared with controlled blood pressure group (n = 30),OP ([285.7 ± 6.2] vs [282.2 ± 5.2];P = .012) of uncontrolled group (n = 38) increased significantly.

Conclusion

Decreased OP and OI, increased BNP and BS are early predictors for severe COVID-19 patients with hypertension.For poorly controlled blood pressure,targeting RAS and OP,early use of RAS inhibitors or combination with loop diuretics may be an effective treatment.

Background

Since the outbreak of coronavirus disease 2019 (COVID-19) caused by an officially named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the number of confirmed cases has increased and

spread rapidly to most countries around the world [1]. Among patients admitted to a hospital, emerging data suggest that hypertension may be associated with an up to 2.5-fold higher risk of severe and fatal COVID-19,especially among older individuals [2]. However, the exact pathogenesis and early clinical predictors of severe COVID-19 with hypertension are rarely reported [3, 4], which undoubtedly has a serious impact on the early realization of risk stratification and optimized therapeutic intervention.

It is well known that SARS-CoV-2 uses the host protein Angiotensin Converting Enzyme 2 (ACE2) as a coreceptor to gain intracellular entry into human alveolar epithelial cells [5, 6].ACE2 is a key enzyme component of renin-angiotensin -aldosterone system (RAS), which degrades angiotensin II (a peptide with multiple effects that promote hypertension) and produces angiotensin 1–7,thereby antagonizing the role of angiotensin II [7]. In fact,ACE2 expression is down-regulated after SARS-COV-2 infection.In addition to blood pressure regulation, RAS also plays an important role in water and sodium metabolism and osmotic pressure (OP) regulation.Clinically, the vast majority of severe COVID-19 with hypertension are caused by acute respiratory distress syndrome (ARDS).However, limited by insufficient data to support,the role of water and sodium metabolism and OP in the pathogenesis of ARDS remains uncertain and needs to be clarified. Our research aims to identify early predictors of severe COVID-19 with hypertension,explore antihypertensive drugs with potential therapeutic effects from the perspective of water and sodium metabolism and OP regulation, and provide a basis for clinical prediction and treatment decisions.

Materials And Methods

Definition and classification

Referring to the National Institute for Health and Clinical Excellence (NICE) 2019 guidelines for hypertension [8], hypertension is based on the following two definitions: (a) Self-reported previous hypertension;(b) Newly comfirm diagnosed hypertension: clinic systolic blood pressure (SBP)/diastolic blood pressure (DBP) of 140/90 mmHg or higher. The goal of hypertension control is to reduce the clinic blood pressure to below 140/90 mmHg for adults aged under 80 and 150/90 mmHg for age over 80,and maintain that level.The oxygenation index (OI) is the ratio of arterial oxygen partial pressure (PaO2) and fraction of inspired oxygen (FiO2).Referring to the guidelines on the diagnosis and treatment of 2019 novel coronavirus infected pneumonia (the sixth edition draft) issued by the National Health Commission of China [9], patients were clinically classified.The details are as follows: (a) Mild: clinical symptoms are mild, and there is no pneumonia manifestation in imaging.(b) Ordinary:It has fever, respiratory tract and other symptoms.Pneumonia can be seen on imaging. (c) Severe: meets any of the following: shortness of breath;respiratory rate (RR) > 30 times/min at rest;refers to oxygen saturation < 93%;OI < 300 mmHg(l mmHg = 0.133 kPa);lung imaging shows the progress of lesion was > 50% at 24–48 h. (d) Critical: one of the following conditions: respiratory failure and mechanical ventilation; shock; combined with failure of other organs should be treated in the Intensive Care Unit.Abnormal liver function (ALF) is defined as total bilirubin > 21 μmol/L (reference range:1.7–21) or alanine aminotransferase > 45U/L (reference range:0–45) or aspartate aminotransferase > 45U/L (reference range: 0–45).Abnormal renal function (ARF) is defined as creatinine above the upper limit (reference range:0.6–1.2 for male, 0.55–1.1 mg/dL for

female).Elevated B-type natriuretic peptide (BNP) is defined as N-terminal pro-brain natriuretic peptide (NT-proBNP) (reference range: 0-125 for age under 75, 0-450 ng/L for age over 75) or BNP (reference range: 0–23 pmol/L) above the upper limit .

Data collection

For all included cases, we retrieved electronic medical records and retrospectively analyzed clinical and laboratory data on the first day of admission. According to the final clinical diagnosis classification, it is divided into non-severe group (mild + ordinary) and severe group (severe + critical). Inclusion criteria: all confirmed COVID-19 cases with hypertension.Exclusion criteria: cases with missing data or withdrawing from other diseases.

Statistical Analysis

All analyses were conducted by using of IBM Statistical Product and Service Solutions software Version 24 (SPSS Inc,Chicago,IL).Continuous variables were summarized as the median with their interquartile ranges (IQRs) or mean with standard deviations (SDs), median [IQR] or [mean ± SD], depending on whether their distributions were normal or not.Comparisons of categorical variables were performed using the Pearson Chi-square test.95% confidence intervals (CIs) were calculated if applied.The parametric tests (independent sample Student t-test or One-way analysis of variance) or non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test) were used to analyze variables.Variables with $P < 0.1$ were entered into a multivariate binary logistic regression model.Model fitness was assessed with the Hosmer-Lemeshow goodness-of-fit test.Analysis of the area under curve (AUC) of receiver operating characteristic (ROC) was constructed to assess the predicting performance..$P < .05$ was considered as statistically significant in all tests if applied.

Results

From Jan 22nd to Mar 31st, a total of 70 COVID-19 patients with hypertension were admitted to the hospital,1 (1.4%) case with cerebellar infarction and 1 (1.4%) case with uremia combined with acute heart failure during hospitalization was excluded. Of the 68 included cases, the final clinical diagnostic classification was 27 (39.7%) for severe and 41 (60.3%) for non-severe.

Between non-severe group (n=41) and severe group (n=27), the number of fever (78% vs 96.3%;P=.043),elevated BNP (4.9% vs 29.6%;P=.011) and ARF (9.8% vs 25.9%;P=.099),and albumin ([42.7±3.1] vs [40.5±3.7];P=.008),lactate dehydrogenase (LDH) (269[188-408] vs 385[243.5-532.5];P=.031),ultrasensitive troponin I (TnIUltra) (0.012[0.006-0.012] vs 0.012[0.012-0.015];P=.004),PH Value ([7.42±0.02] vs [7.44±0.03];P=.016),arterial carbon dioxide partial pressure ($PaCO_2$) ([37.9±3.4] vs [35.8±4.3];P=.025),sodium ([139.5±2.9] vs [136.5±3.2];P=.000), osmotic pressure (OP) ([285.9±5.4] vs [281.2±5.8];P=.001), blood sugar (BS) (5.9[5.5-6.7] vs 7.7[6.3-8.5];P=.009) and OI ([395±62] vs [326±95];P=.002) have obvious differences. While age ([59.8±11.3] vs [63.6±8.4];P=.136), male gender (56.1% vs 70.4%;P=.315), comorbidities with diabetes or atherosclerotic cardiovascular disease (ASCVD),

smoking history,number of ALF,heart rate (HR),respiratory rate (RR),SBP,DBP,white blood cell (WBC) count,hematocrit (HCT),potassium and lactic acid are statistically insignificant (Table 1).

All variables with P <0.1 were entered into a backward stepwise multivariate logistic regression model, and the last step was to obtain four independent predictors of BNP (P=.026),OP (P=.004),BS (P=.017) and OI (P=.001) (Table 2).Goodness of fit testing (Hosmer-Lemeshow test) was used to assess deviations between observed and expected values. A P value of >.05 implies no significant difference between the observed and expected values.The P value of the goodness-of-fit testing of our model is 0.739, and therefore it is acceptable (Figure 1).Analysis of the AUC of the ROC curve was constructed to assess the predicting performance.The AUC of model is 0.904 ([95%CI] [0.832-0.976];P=.000),with excellent performance. BNP, OP, BS or OI as a single predictor, their AUC are 0.624, 0.726, 0.687 and 0.75 respectively (Table 3).

According to previous use of antihypertensive drugs before admission, 68 cases were divided into a blank control group (n=27).A: RAS inhibitors group (n=21),consisting of 4 cases of ACEIs with or without calcium channel blockers (CCB) and 17 cases of ARBs with or without CCBs. B: The other antihypertensive drugs group (n=20),consisting of 3 cases of beta receptor blockers, 12 cases of CCBs and 5 cases of combinations.Compared between three groups,OP (P=.020) had significant differences.Among them,compared with control group and group B, OP ([287.3±5.7] vs [283.5±6.1];P=.045) ([287.3±5.7] vs [281.9±5.4];P=.007) in group A has increased significantly. While HR, SBP, DBP, severe ratio, number of elevated BNP, BS and OI were insignificantly different (Table 4).

According to blood pressure measured at the time of admission and control target, the included cases were divided into controlled blood pressure group (n=30) and poorly controlled blood pressure control group (n=38).Compared with controlled group,OP ([285.7±6.2] vs [282.2±5.2];P=.012) of poorly controlled group increased significantly, while severe ratio,number of elevated BNP,BS and OI had no significant difference (Table 5).

Discussion

The pattern of lung injury caused by SARS-CoV-2 is called diffuse alveolar injury,which is a histological change associated with ARDS. Undoubtedly, systemic water and sodium retention and reduced OP will lead to edema and exudation of alveolar epithelial cells, alveolar collapse, and promote the development of ARDS.The body's water and sodium metabolism balance and OP regulation mainly through the following three neuroendocrine systems:(a) RAS.(b)Antidiuretic hormone (ADH).(c)Natriuretic peptide. Conversely,SARS-CoV-associated pneumonia can aggravate water and sodium retention and OP reduction.The possible pathogenesis is as follows: (a) ACE2 is mainly produced in type II alveolar epithelial cells.The damage associated with SARS-CoV infection seriously impairs the production of ACE2.Down-regulated ACE2 results in excessive activation of RAS [10, 11].In addition,accumulated angiotensin II can also promote secretion of ADH.(b) Syndrome of inappropriate ADH secretion,pulmonary infections may be accompanied by excessive secretion of ADH [12]. Our observed COVID-19 cases with hypertension generally have different levels of decreased sodium,OP and OI, and increased BNP at the

beginning of admission, and the later cases of increased severity have lower OP and OI. This suggests that water and sodium retention,OP reduction and diffuse alveolar injury occurred in the early stage of COVID-19, which may be one of the initiating factors for the development of ARDS.Moreover, insulin resistance and stress hyperglycemia may also be involved [13].

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the first-line drugs widely used in patients with hypertension[14]. However, whether to continue to use ACEI/ARB in the setting of COVID-19 has caused widespread controversy [10, 11].The continuous management of ACEI/ARB may prevent excessive activation of RAS by preventing ACE2 down-regulation, which is beneficial to reduce the risk of ARDS [7, 15]. In addition, most hypertension itself has high RAS activity.Both hypertension and pharmacological RAS inhibition will increase ACE2 levels, which may increase human susceptibility and theoretically promote SARS-CoV-2 invasion and infection proliferation [10, 11].The downregulation of ACE2 after SARS-CoV-2 infection will accelerate the destruction of RAS axis balance.Excessive accumulation of angiotensin II,and ADH will increase retention of water and sodium and decrease OP, which will conversely increase hypertension and further promote the progress of ARDS.This may be why COVID-19 patients with hypertension is more likely to increase severity.In theory, these patients should choose RAS inhibitors. In our study, there was no significant difference in blood pressure at admission of patients who had previously used RAS inhibitors and had no effect on the later increased severity,but OP increased significantly.This subtle change suggests that the protective effect of RAS inhibitors may far exceed its own antihypertensive property, which is consistent with related reports [16, 17]. The OP of patients with poorly controlled blood pressure is also elevated, and this seemingly contradictory result seems to suggest that antihypertension is not necessary.However, the increase in blood pressure in the early stages of the disease is more likely to be a passive increase, which is also a manifestation of high RAS activity. Insignificant difference of poorly controlled blood pressure and use of RAS inhibitors on severe ratio may be related to the sample size being too small to reflect.Moreover,poorly controlled blood pressure obviously increases the cardiopulmonary burden and promotes an increase in severity.Therefore,early use of RAS inhibitors in COVID-19 patients with poorly controlled blood pressure is very important.

At present, in addition to traditional RAS inhibitors [7, 15, 16], some new drugs targeting the RAS axis have appeared. Recombinant human ACE2 (rhACE2) protein may play an important role in protecting ARDS patients [17],and has achieved good therapeutic effects in animal models and has entered clinical trials [18, 19].The latest research data shows that recombinant human soluble (hrsACE2) can directly inhibit SARS-CoV-2 infection in engineered human blood vessel organoids and human kidney organoids, blocking the early stage of infection [20].In theory, systemic administration of hrsACE2 can neutralize SARS-CoV-2 and avoid the damage of alveolar epithelial cells caused by direct virus invasion, which has significant clinical application value. Targeted OP, loop diuretics may be a very effective treatment option. In addition, tolvaptan, a diuretic that has been used clinically, as an ADH type-2 receptor antagonist, may also have certain clinical application prospects.

There are several limitations in our retrospective cohort study. First, due to the small sample size of the single-center research hospital, there may be sampling errors. Second, the patients may be in different stages of COVID-19 when they are admitted to the hospital.Third, the activity and concentration of RAS and ADH in plasma were not detected at the time of admission,our results are not convincing enough. Therefore,these results should be carefully interpreted owing to potential selection bias and residual confounding. Large prospective randomized clinical trials in countries around the world may also be needed to provide further data support.

Conclusions

COVID-19 with hypertension generally have different levels of decreased OP and OI. Decreased OP and OI, increased BNP and BS are early predictors for severe COVID-19 with hypertension.RAS inhibitors can increase the OP of COVID-19 with hypertension.For poorly controlled blood pressure,targeting RAS and OP ,early use of RAS inhibitors or combination with loop diuretics may be an effective treatment.

List Of Abbreviations

ACE,Angiotensin-converting enzyme;ACEI,Angiotensin-converting enzyme inhibitor;ADH,Antidiuretic hormone;ALF,Abnormal liver function; ARB,Angiotensin II receptor blocker;ARDS,Acute respiratory distress syndrome; ARF,Abnormal renal function; ASCVD,Atherosclerotic cardiovascular disease; AUC, area under curve;BNP,B-type natriuretic peptide;BS,blood sugar;CCB,Calcium channel blocker;CI,confidence interval;COVID-19,coronavirus disease 2019; DBP,Diastolic blood pressure;FiO2,fraction of inspired oxygen; HCT,Hematocrit;HR,heart rate; LDH,lactate dehydrogenase;NT-proBNP,N-terminal pro-brain natriuretic peptide;OI,Oxygenation index;OP,Osmotic pressure; PaCO2,arterial carbon dioxide partial pressure;PaO2,arterial oxygen partial pressure; RAS,Renin-angiotensin -aldosterone system;ROC,receiver operating characteristic curve;RR,Respiratory rate;SaO2,Oxyhemoglobin saturation;SARS-CoV-2,Severe acute respiratory syndrome coronavirus 2;SBP, Systolic blood pressure;SD,standard deviation;SE,standard error; SIADH,Syndrome of inappropriate antidiuretic hormone secretion; TnIUltra,ultrasensitive troponin I;WBC, white blood cell.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of The Third People's Hospital of Shenzhen (approval number:2020-173). Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements. Verbal informed consent was obtained from all participants.Permission in access to all raw data supporting the conclusions of this retrospective study are granted by the Scientific Research Committee of The Third People's Hospital of Shenzhen.

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

Conceptualization and design: DP,YG

Formal analysis and investigation: DP, YG,ZZ,AT,HW

Data curation: AT, ZZ,HW

Writing - original draft: YG, ZZ

Writing - review & editing: DP

Approval of the final manuscrip: DP,YG, ZZ,AT,HW

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Tables

Table 1:Univariate comparison between Non-severe and Severe group

Items	Non-severe (n=41)	Severe (n=27)	P Value
Age: (years)	59.8±11.3	63.6±8.4	0.136
Male gender:n(%)	23 (56.1%)	19 (70.4%)	0.315
Diabetes:n(%)	5 (12.2%)	5 (18.5%)	0.502
ASCVD:n(%)	24 (58.5%)	21 (77.8%)	0.122
Smoking history:n(%)	3 (7.3%)	1 (3.7%)	1.000
Number of elevated BNP: n(%)	2 (4.9%)	8 (29.6%)	0.011
Number of ALF: n(%)	10 (37%)	5 (22%)	0.269
Number of ARF: n(%)	4 (9.8%)	7 (25.9%)	0.099
HR: (times/min)	86±15	90±8	0.136
RR: (times/min)	20 (20-20)	20 (19-22)	0.747
SBP: (mmHg)	139.2±16.4	143.3±20.8	0.363
DBP: (mmHg)	85.8±11.5	86.9±13.3	0.720
WBC: (×10^9/L) (3.5-9.5)	5.1 (3.8-6.9)	5.1 (3.8-6.3)	0.666
HCT: (%) (37-52)	39.7±4.5	39.9±3.3	0.899
Albumin:(g/L) (40-55)	42.7±3.1	40.5±3.7	0.008
LDH: (U/L) (120-250)	269 (188-408)	385 (243.5-532.5)	0.031
TnIUltra: (µg/L) (0-0.034)	0.012 (0.006-0.012)	0.012 (0.012-0.015)	0.004
PH Value: (7.35-7.45)	7.42±0.02	7.44±0.03	0.016
$PaCO_2$: (mmHg) (35-45)	37.9±3.4	35.8±4.3	0.025
Sodium: (mmol/L) (135-145)	139.5±2.9	136.5±3.2	0.000
Potassium: (mmol/L) (3.5-5.5)	3.6±0.3	3.5±0.3	0.795
OP: (mOSM/L) (290-310)	285.9±5.4	281.2±5.8	0.001
BS: (mmol/L) (3.9-6.1)	5.9 (5.5-6.7)	7.7 (6.3-8.5)	0.009
	1.3 (1.1-1.5)	1.4 (1.15-1.8)	0.584
	395±62	326±95	0.002

Lactic acid: (mmol/L) (0.5-1.5)				
OI: (mmHg) (400-500)				

Table 2:Independent predictors for severe COVID-19 with hypertension

Items	P Value	B	Exp(B)	95%CI
BNP	0.026	2.51	12.307	1.349-112.251
OP	0.004	-1.064	0.345	0.169-0.705
BS	0.017	0.816	2.262	1.158-4.422
OI	0.001	-1.319	0.267	0.124-0.577

Table 3: Predicting performance for severe COVID-19 with hypertension

Items	AUC	SE	P Value	95%CI
Model	0.904	0.037	0.000	0.832-0.976
BNP	0.624	0.072	0.086	0.482-0.765
OP	0.726	0.063	0.002	0.603-0.85
BS	0.687	0.069	0.009	0.553-0.821
OI	0.750	0.060	0.001	0.632-0.869

Table 4:Impact of antihypertensive drugs on COVID-19 with hypertension

Items	Control (n=27)	A (n=21)	B (n=20)	P Value
SBP: (mmHg)	139.1±18.8	145.1±20.8	138.7±14.4	0.444
DBP: (mmHg)	83.6±12.4	89±13.5	87±10.1	0.302
HR: (times/min)	89±14	83±13	90±11	0.154
Severe ratio: n (%)	10 (37%)	7 (33.3%)	10 (50%)	0.516
Number of elevated BNP:n(%)	5 (18.5%)	3 (14.3%)	2 (10%)	0.716
OP: (mOSM/L) (290-310)	283.5±6.1	287.3±5.7	281.9±5.4	0.020,0.045*,0.007**
BS: (mmol/L) (3.9-6.1)	6(5.6-8.4)	6.5(6-7.8)	6.2(5.3-7.1)	0.405
OI: (mmHg) (400-500)	357(335-422)	388(348-409)	371(335-404)	0.593

A:ACEI/ARB with CCB or without CCB;B:Beta receptor blocker and or CCB;*A Vs Control;**A Vs B

Table 5:Impact of blood pressure control on COVID-19 with hypertension

Items	Controlled (n=30)	Uncontrolled (n=38)	P Value
Severe ratio: n (%)	12 (40%)	15 (39.5%)	1.000
Number of elevated BNP:n(%)	4 (13.3%)	6 (15.8%)	1.000
OP: (mOSM/L) (290-310)	282±5.2	285.7±6.2	0.012
BS: (mmol/L) (3.9-6.1)	6.5 (5.4-8.1)	6.3 (5.7-7.6)	0.757
OI: (mmHg) (400-500)	370.2±106.8	365.1±60.3	0.815

Figures

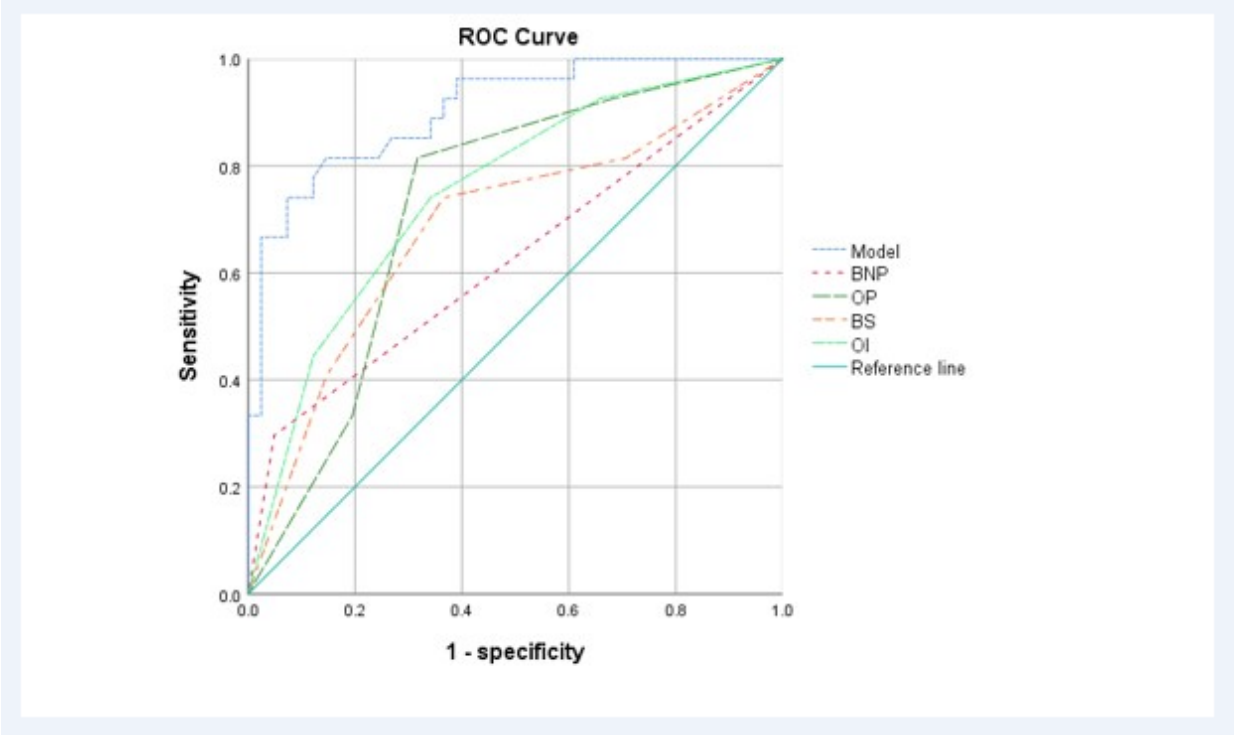

Figure 1

The AUC and the P value of Hosmer-Lemeshow testing of model is were 0.904 and 0.739, respectively.