A preoperative nomogram for sepsis in percutaneous nephrolithotomy treating solitary, unilateral, and proximal ureteral stones

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BACKGROUND: Postoperative sepsis is a lethal complication for percutaneous nephrolithotomy (PCNL). An early predictive model combined local and systemic conditions is urgently needed to predict infectious events. We aim to determine the preoperative predictors of sepsis after PCNL in patients with unilateral, solitary, and proximal ureteral stones.

METHODS: A total of 745 patients who underwent PCNL between January 2012 and December 2018 were retrospectively enrolled. Sepsis was defined based on the International Sepsis Definitions in 2001, and the preoperative factors were compared between the non-sepsis and sepsis groups. Univariable analysis and multivariable logistic regression analysis were conducted to determine the predictors for sepsis after PCNL. A nomogram was generated using the predictors.

RESULTS: In this study, 35 patients (4.7%) developed sepsis after PCNL. Univariate analysis showed that post-PCNL sepsis was associated with the female, lower albumin, higher globulin, lower albumin globulin ratio (AGR <1.5), preoperative fever, leukocytosis (WBC ≥10,000 cells/µL), positive urine culture, leukocyturia (≥50 cells/µL) and positive urine nitrite. Multivariate logistic regression analysis suggested that AGR <1.5 (odds ratio [OR]=5.068, 95% confidence interval [CI]=1.135-22.624, P = 0.033), positive urine culture (OR=3.243, 95% CI=1.162-9.047, P =0.025), leukocytosis (OR=3.706, 95% CI=1.444-9.512, P =0.006), and female (OR=2.529, 95% CI=1.127-5.672, P =0.024) were independent risk factors for sepsis. A nomogram was generated and displayed favorable fitting (Hosmer-Lemeshow test P =0.797), discrimination (area under receiver operating characteristic curve was 0.807), and clinical usefulness by decision curve analysis.

CONCLUSIONS: Patients with certain preoperative characteristics, such as female, lower AGR, positive urine culture, and leukocytosis, who undergo PCNL may have a higher risk of developing sepsis. A cautious preoperative evaluation and optimized treatment strategy should be considered in these patients to minimize infectious complications.

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Abstract

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36 cells/ μ L), positive urine culture, leukocyturia ($\geq$50 cells/ μ L) and positive urine nitrite.
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Introduction

50   Urolithiasis is a common urologic disease with a prevalence rate of 5.8% in the general
51 population, and the recurrence rate has been shown to reach 60% within 10 years [1,2]. The
52 treatment options for stone disease range from open surgery to endoscopic surgery, such as
53 percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS) [3]. Generally, PCNL results in
54 higher stone-free rate than URS, at the expense of elevated complication rate and prolonged
55 hospital stays, without difference in secondary interventions [4,5]. However, infection remains a
56 main complication that can cause longer length of stay and even lethal sepsis shock [6]. Therefore,
57 establishing a predictive model, especially in the early stages of hospitalization, is imperative to
58 help develop prevention strategies.
59 The risk factors for sepsis after PCNL were systematically summarized [6]. The preoperative
60 factors comprised the following: positive urine culture, female sex, nephrostomy, urinary
61 diversion, stone size, hydronephrosis, diabetes, and complicated stone. Among these, the local
62 urological condition is considered to be a critical factor related to infectious complications.
63 Additionally, new factors for infection have emerged in recent years. These factors, such as C-
64 reactive protein, albumin, and procalcitonin, show strong predictive value by reflecting the
65 systematic condition of the patient [7,8].
66   Currently, a preoperative model, integrating local and systematic conditions, is scarce to
67 evaluate the probability of sepsis. The purpose of this study was to analyze post-PCNL sepsis in
68 solitary, unilateral, and proximal ureteral stone patients. Furthermore, the results of this study
69 were used to develop a preoperative risk factor nomogram that may help urologists identify
70 patients who are more likely to develop sepsis.
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Materials & Methods

75   The study was conducted under the approval of the Ethics Committee of Tongji Medical
76 College, Huazhong University of Science and Technology (2019S1035). We retrospectively
77 enrolled 745 patients who underwent PCNL from January 2012 to December 2018. The
78 inclusion criteria were the following: (1) PCNL was performed to treat unilateral, solitary, and

79   proximal ureteral stones; and (2) age ⩾18 years. Stones size bigger than 10mm. The exclusion

80   criteria were anatomical renal abnormalities (horseshoe kidney, solitary kidney, transplant

81   kidney, and kidney duplication). Patients imaging, including abdominal computed tomography

82   CT, confirmed the presence and size of proximal ureteral stones (above the fourth lumbar spine

83   or in the ureteropelvic junction). Types of anesthesia, preoperative antibiotics, surgeons' years'

84   experience, PCNL operation details were identified and recorded. Postoperative patients' data

85   were revised, collected, and recorded.

86   Patients information were collected from our hospital's database, including age, sex, body

87   mass index (BMI), comorbidities (diabetes, hypertension, and coronary heart disease), stone size

88   and laterality, prior indwelling stent, blood tests (cholesterol, creatinine, albumin, and globulin

89   levels and white blood cell count), fever (defined as body temperature >38°C), urine tests (white

90   blood cell and nitrite), urine culture, and ASA score.

91   Sepsis was defined according to the 2001 International Sepsis Definitions Conference;

92   occurrence of an infection and a minimum of two of the following within 48 hours of surgery:

93   (1) heart rate >90/minute, (2) body temperature >38°C, (3) leukocyte count <4,000 cells/μL or

94   >12,000 cells/μL, and (4) respiratory rate >20/minute [9].

95   All statistical analyses were performed using SPSS 24.0 and R software 3.6.2. The cut-off

96   value was determined by the Youden Index. The student t-test was used to detect differences

97   between continuous variables with a normal distribution. The chi-square test or Fisher's exact

98   test was used to compare categorical variables. The multivariable logistic regression method was

99   used to determine independent risk factors for sepsis. Then predictive nomogram was generated

100   based on converting the regression coefficient to a 0- to 100-point scale proportionally. The

101   predictive performance of the model was measured by validation, discrimination and decision

102   analysis[10]. A calibration curve was generated with 1000 bootstrap samples to reduce the overfit

103   bias. Hosmer-Lemeshow (HL) test implied good calibration when the test is insignificant. The

104   discriminative performance was assessed by area under the receiver operating characteristic

105   (ROC) curve. The clinical usefulness of the nomogram is evaluated by decision curve analysis

106   (DCA) by assessing net benefits at different threshold probabilities. P-value <0.05 was

107   considered significant.

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Results

112   We identified 745 patients who underwent PCNL for a solitary, unilateral, and proximal

113   ureteral stone, and 35 patients developed sepsis. The patients' demographic details and

114   univariable analysis results of risk factors are shown in Table 1. No patients were concomitant

115   with paraplegia. The characteristics of patients who developed sepsis included female sex, lower

116   albumin, higher globulin, lower AGR (<1.5), preoperative fever, leukocytosis (WBC ⩾10,000

117   cells/μL), positive urine culture, leukocyturia (⩾50 cells/μL), and positive urine nitrite.

118   Notably, stone size and operation time were comparable between the two groups. The stone
119   shape is rotundity or extension.
120   In the multivariate analysis, four factors were identified as independent factors for sepsis:
121   AGR <1.5 (odds ratio [OR]=5.068, 95% confidence interval [CI]=1.135-22.624, P = 0.033),
122   positive urine culture (OR=3.243, 95% CI=1.162-9.047, P =0.025), leukocytosis (OR=3.706,
123   95% CI=1.444-9.512, P =0.006), and female sex (OR=2.529, 95% CI=1.127-5.672, P =0.024)
124   (Table 2). Furthermore, we categorized AGR into 3 groups: ≥1.5, 1.0-1.5, and <1.0. Figure 1
125   shows an increasing sepsis rate with increasing levels: 0.78% (2/255), 5.93% (25/421), and
126   11.59% (8/69), respectively.
127   Based on the multivariable analysis, a nomogram prediction model was established to
128   calculate the cumulative probability of sepsis after PCNL (Figure 2). The total points were
129   obtained by adding the points assigned to the four factors. The corresponding sepsis rate is
130   indicated by the total points axis. The calibration curve showed good fitting of the model with no
131   statistical significance (P =0.797) through the Hosmer-Lemeshow test (Figure 3-A). The ROC
132   curve illustrated favorable discrimination with an area under the curve of 0.807 (Figure 3-B).
133   The DCA of the model showed a threshold probability of 10-90% (Figure 4), in which the model
134   had the ability to identify stone patients who might develop sepsis after PCNL superior to the
135   "treat-all-patients" or "treat-none" schemes.
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137

138   **Discussion**
139   Compared with other minimally invasive lithotripsy techniques, PCNL is generally considered to
140   be a safe technique that offers the highest stone-free rates [11,12]. However, complications still
141   occur following this percutaneous procedure. With the advancements in technology in recent
142   years, the safety of PCNL has been effectively improved. However, infection is still one of the
143   main complications. The sepsis rate reached 4.7% (35/745) in our research, which was consistent
144   with previous studies (0.9%-5.9%) [13,14]. Once the infection further deteriorates without timely
145   recognition and intervention, it may lead to life-threatening complications, like shock and organ
146   dysfunction. Therefore, the early determination of factors associated with sepsis complications is
147   critical to avoid serious postoperative events. In this study, we developed a nomogram utilizing
148   the four preoperative characteristics from multivariate analysis: sex, AGR, urine culture, and
149   blood WBC. This preoperative predictive model combined both local and systematic conditions
150   to evaluate the probability of sepsis.
151   Interestingly, our study revealed that AGR (<1.5) is an independent predictor of post-PCNL
152   sepsis (RR=5.068, P = 0.033). A low AGR is mainly used as a predictor of cancer progression
153   and cancer-related mortality [15]. AGR mainly reflects the changes in plasma albumin and globulin
154   levels. Among them, albumin is used to reflect the nutritional status and systemic inflammatory
155   response; a lower level of albumin leads to the insufficient synthesis of immunoglobulin, which
156   weakens the immune system [16]. Yang et al. reported that a low-normal level of serum albumin
157   before surgery predicts post-PCNL fever [17]. Xu et al. demonstrated that the preoperative high-

158 sensitive C-reactive protein/albumin (hs-CRP/Alb) ratio is independently predictive for the
159 development of systemic inflammatory response syndrome after PCNL [18]. Usually, globulin
160 plays an important role in immunity and inflammation. In the early phase of infection, the
161 immunoglobulin level elevated rapidly [19], which may account for the results in our study. A low
162 AGR may indicate a susceptible state to infection. PCNL surgery brings about a stress response
163 and backflow of pathogens and toxins, which accelerates the spread of infection and further leads
164 to the occurrence of sepsis. Unlike other studies that only focus on local factors [20,21], our study
165 found that AGR, a systemic factor, maybe one of the important predictive factors of sepsis after
166 PCNL.
167 Another systemic factor noted in our study to be closely related to sepsis after PCNL is
168 preoperative leukocytosis (RR=3.706, P =0.006). Mahmood et al. reported that preoperative
169 leukocytosis is associated with adverse postoperative outcomes after cardiac surgery and is an
170 independent predictor of infection-related postoperative complications [22]. Sen et al. found that
171 the preoperative neutrophil-lymphocyte ratio may be a promising additive predictor of
172 bacteremia and postoperative sepsis in patients who undergo PCNL for renal stones [23]. However,
173 Bozkurt et al. presented a different view on the relationship between postoperative leukocytosis
174 and sepsis. Their study showed that postoperative leukocytosis is common after PCNL and
175 represents a normal physiologic response to surgery [24]. Preoperative leukocytosis may indicate
176 the existence of potential infection in the body. The stress reaction and trauma caused by PCNL
177 surgery may lead to the aggravation of infection, and thus, resulting in sepsis.
178 As a usual local urological condition, positive urine culture is considered as a critical factor
179 related to infectious complications after a PCNL operation [17,25]. It is in conformity with our result
180 that the risk of sepsis was found to be increased by more than three times in patients with
181 positive urine culture. PCNL may cause vascular injury and high intrarenal pressure. For patients
182 with a positive urine culture, this operation can promote the invasion of blood circulation by
183 local pathogens and toxins and lead to the occurrence of sepsis. In our study, bladder urine was
184 used for the urine culture examination. Emerging studies concluded that stone culture[26,27] and
185 pelvic urine culture[27] were better predictors of urosepsis than mid-stream bladder urine culture.
186 However, sample from kidney and stone cannot be obtained until surgery starts, which limits
187 their early predictive and preventive value. Mid-stream bladder urine culture is still the optimal
188 predictor that can be early acquired.
189 In our study, female sex was also found to be an independent predictor for sepsis after PCNL
190 (RR=2.529, P =0.024). Similarly, many studies have reported that female sex was significantly
191 associated with post-URS or post‐PCNL SIRS [18,25,28]. Martov et al. from the CROES URS
192 Global Study showed that female sex was a significant risk factor of postoperative urinary tract
193 infection or fever in patients with a negative baseline urine culture [29]. Female is more susceptible
194 to urinary tract infection than male, which may be one of the reasons why female sex is prone to
195 sepsis after PCNL[30]. Additionally, sex-related gene polymorphisms[31] and the effects of sex
196 hormones[32] may be other potential pathomechanisms to account for the susceptibility to sepsis
197 after PCNL of the female sex.

198 Our study had certain limitations. First, this study was a retrospective study performed at a single
199 center, which may have led to potential selection bias. Second, only patients with proximal
200 ureteral stone were enrolled considering homogeneous stone characteristics. Further research
201 will investigate various kidney stone to verify the risk factors of sepsis. Third, although the
202 model established in this study revealed favorable fitting, discrimination, and clinical usefulness,
203 external validation is lacking, which is expected to be testified in independent cohorts. It is the
204 first study to reveal the predictive value of the preoperative AGR for post‑PCNL sepsis.
205 However, the specific underlying mechanism remains unclear. A prospective study is planning to
206 uncover the septic risk with more precise variables.
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208

Conclusions

210 A new nomogram is developed to predict sepsis in PCNL for an upper ureteric single stone if the
211 patient has these characters: female sex, lower AGR, positive urine culture, and leukocytosis.
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Acknowledgments

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Table 1: Patients characteristics and univariable analysis of risk factors for post-operative sepsis after percutaneous nephrolithotomy.

1   Table 1: Patients characteristics and univariable analysis of risk factors for post-operative sepsis after percutaneous

2   nephrolithotomy.

Variable	Sepsis (n=35)	Non-sepsis (n=710)	*P* value
Age (yr), mean (SD)	49.7 (10.8)	50.7 (12.1)	0.625
BMI (kg/m^2), mean (SD)	23.8(3.7)	23.9 (3.0)	0.863
Operation time (min), mean (SD)	107.6(32.8)	101.6(37.2)	0.349
Sex, n (%)			
Male	11(2.3)	462(97.7)	< 0.001
Female	24(8.8)	248(91.2)	
Stone height, n (%)			
< 20mm	29(4.6)	601(95.4)	0.775
≥ 20mm	6(5.2)	109(94.8)	
Stone laterality, n (%)			
Left	18(4.6)	372(95.4)	0.911
Right	17(4.8)	338(95.2)	
Indwelling stent, n (%)			
Yes	3(6.0)	47(94.0)	0.917
No	32(4.6)	663(95.4)	
Hydronephrosis, n (%)			
Yes	4(2.9)	134(97.1)	0.268
No	31(5.1)	576(94.9)	
Hypertension, n (%)			
Yes	7(3.9)	173(96.1)	0.556
No	28(5.0)	537(95.0)	
Coronary heart disease, n (%)			
Yes	1(7.1)	13(92.9)	1.000
No	34(4.7)	697(95.3)	
Diabetes, n (%)			
Yes	3(4.8)	60(95.2)	1.000
No	32(4.7)	650(95.3)	
Serum cholesterol, n (%)			
<5.17mmol/L	34(5.2)	617(94.8)	0.128
≥5.17mmol/L	1(1.1)	93(98.9)	
Serum creatinine, n (%)			
normal	31(4.9)	602(95.1)	0.541
abnormal	4(3.6)	108(96.4)	
Albumin, n (%)			
<35g/L	10(11.2)	79(88.8)	0.005
≥35g/L	25(3.8)	631(96.2)	
Globulin, n (%)			0.001

<30g/L	12(2.6)	450(97.4)	
≥30g/L	23(8.1)	260(91.9)	
AGR, n (%)			
<1.5	33(6.7)	457(93.3)	< 0.001
≥1.5	2(0.8)	253(99.2)	
Pre-operative fever, n (%)			
Yes	9(17.0)	44(83.0)	<0.001
No	26(3.8)	666(96.2)	
WBC, n (%)			
<10,000 cells/μL	25(3.7)	659(96.3)	<0.001
≥10,000 cells/μL	10(16.4)	51(83.6)	
Urine culture, n (%)			
Positive	13(14.9)	74(85.1)	< 0.001
Negative	22(3.3)	636(96.7)	
Urine WBC, n (%)			
<50 cells/μL	7(1.9)	353(98.1)	0.001
≥50 cells/μL	28(7.3)	357(92.7)	
Urine nitrite, n (%)			
Positive	8(17.8)	37(82.2)	< 0.001
Negative	27(3.9)	673(96.1)	
ASA score, n (%)			0.591
1	18(5.9)	286(94.1)	
2	17(4.0)	408(96.0)	
3	0(0.0)	15(100.0)	
4	0(0.0)	1(100.0)	

3   Abbreviations: BMI, body mass index; SD, standard deviation; AGR, albumin globulin ratio; WBC, white blood cell.

Table 2: Multivariable logistic regression analysis of predictors of sepsis after percutaneous nephrolithotomy.

1   Table 2: Multivariable logistic regression analysis of predictors of sepsis after percutaneous nephrolithotomy.

Variables	B	SE	OR	95%CI	*P* value
Age (yr)	-0.021	0.018	0.979	0.946-1.014	0.240
BMI (kg/m^2)	0.021	0.059	1.021	0.909-1.148	0.720
Operation time (h)	0.273	0.297	1.314	0.734-2.351	0.358
Stone height ≥20mm	0.034	0.502	1.035	0.387-2.768	0.945
Pre-operative fever	0.828	0.476	2.288	0.900-5.820	0.082
Indwelling stent	-0.728	0.684	0.483	0.127-1.844	0.287
Diabetes	-0.010	0.700	0.990	0.251-3.906	0.989
Hydronephrosis	0.214	0.572	1.238	0.404-3.797	0.709
AGR<1.5	1.623	0.763	5.068	1.135-22.624	0.033
Positive urine culture	1.176	0.523	3.243	1.162-9.047	0.025
leukocytosis	1.310	0.481	3.706	1.444-9.512	0.006
Positive urine nitrite	0.052	0.581	1.053	0.337-3.287	0.929
Female	0.928	0.412	2.529	1.127-5.672	0.024
Urine WBC≥50 cells/μ	0.706	0.481	2.026	0.789-5.197	0.142

2   Abbreviations: AGR, albumin globulin ratio; WBC, white blood cell; B, regression coefficient; SE, standard error;

3   OR, Odds Risk; CI, confidence interval.

Figure 1

Categorized albumin globulin ratio (AGR) and corresponding sepsis rate (***P <0.001).
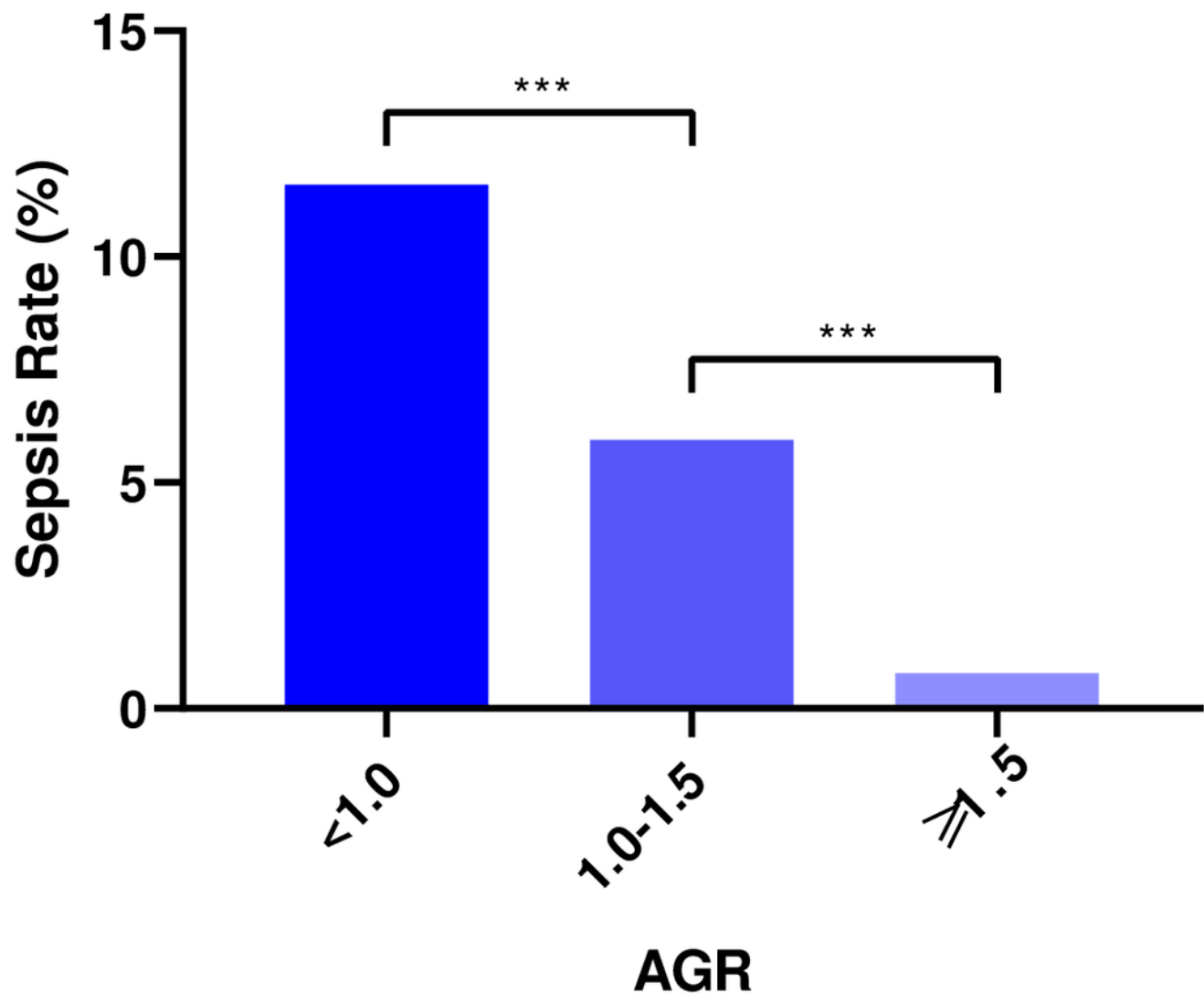
Figure 2

Nomogram for patients predicting post-operative sepsis.

WBC, white blood cell; AGR, albumin globulin ratio. Sex, urine culture, WBC and AGR are marked as "points". Total points by adding the three points can predict sepsis rate.
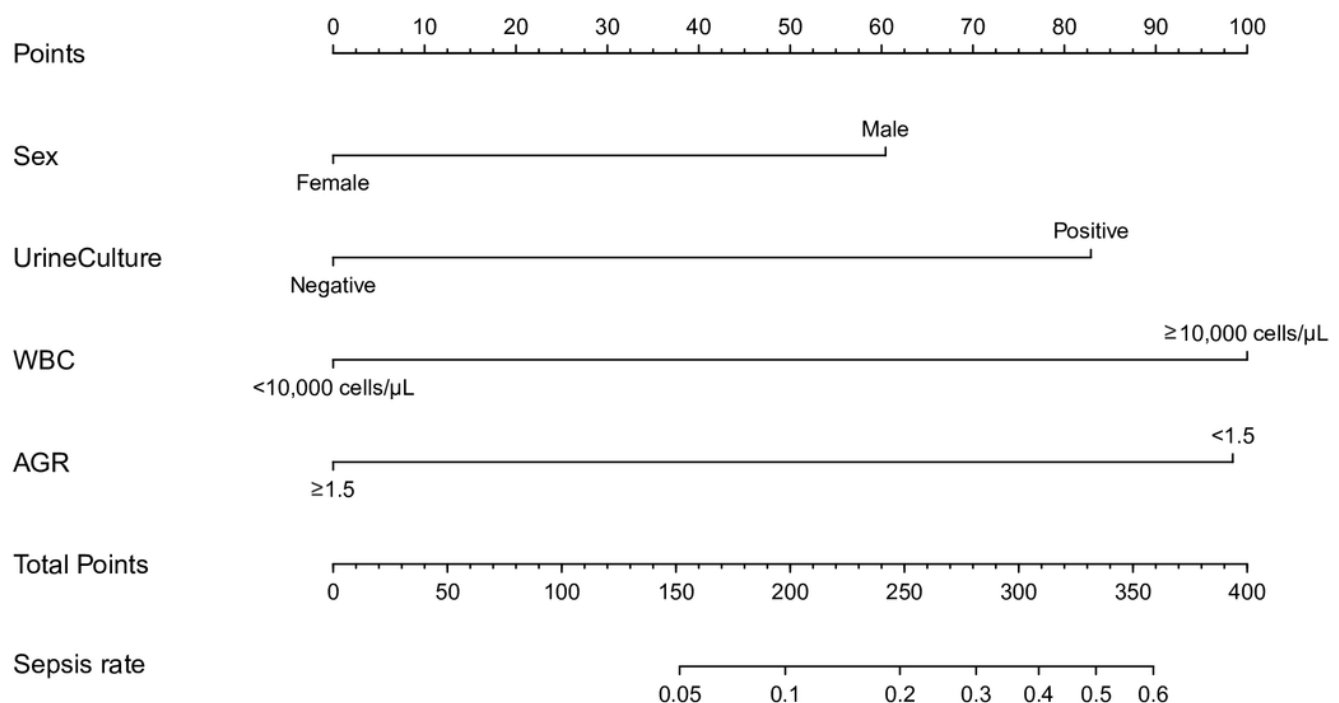
Figure 3

Evaluation of the predictive performance.

(A) Calibration curve. Hosmer-Lemeshow test with insignificant *P* value indicates good fitting of model. (B) Receiver operating characteristic (ROC) curve. The area under curve (AUC) for the model is 0.807, which showed a favorable ability of discrimination.
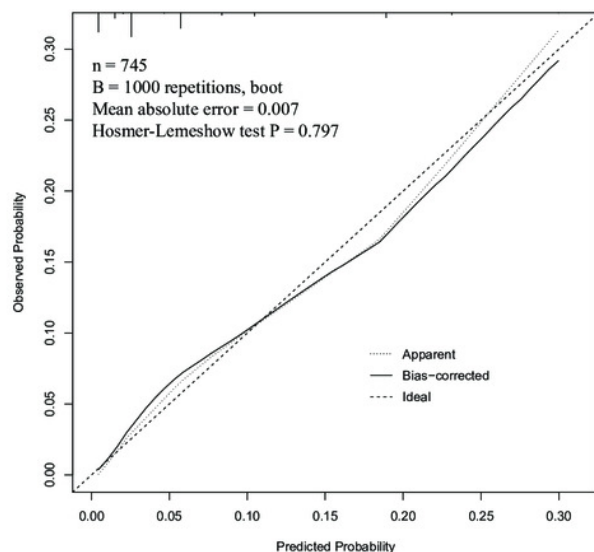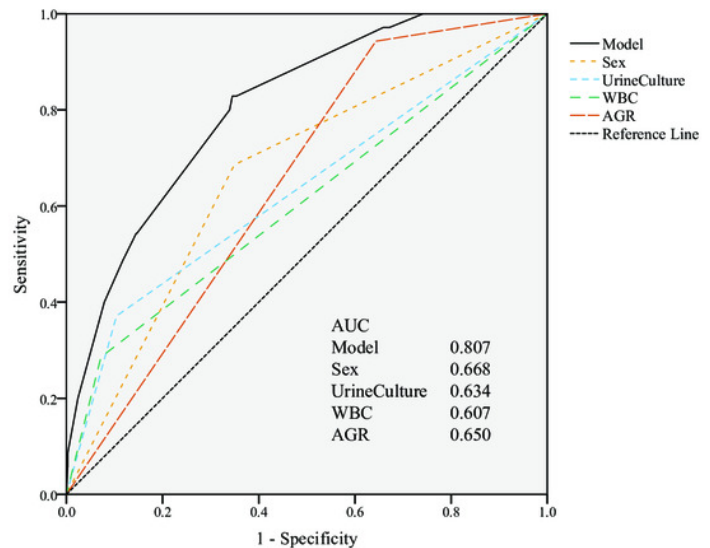
Figure 4

Decision curve analysis (DCA).

When risk threshold is around 10-90%, the net benefit of application of the model on taking measures is greater than "treat-all-patient" or "treat-none" scheme. In addition, utilization of sex, urine culture, white blood cell (WBC) and albumin globulin ratio (AGR) alone is inferior than the model.