

Predictors of Urinary Tract Infection in Acute Stroke Patients: A Case Control Study

Ya-ming Li

Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences

<https://orcid.org/0000-0003-0335-7657>

Yan-xin Zhao (✉ zhao_yanxin@126.com)

Jian-hua Xu

Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences

Research article

Keywords: stroke, infection, prediction, urinary tract infection, hemoglobin, interleukin-6

Posted Date: June 27th, 2019

DOI: <https://doi.org/10.21203/rs.2.10766/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Patients with stroke have a high risk of infection which may be predicted by methods. The methods can reduce unfavourable outcome by preventing the occurrence of infection. Therefore, we aim to identify early predictors for urinary tract infection in patients after stroke. Methods In 186 collected acute stroke patients, we divided them into urinary tract infection group, other infection type groups, and non-infected group. Data were recorded at admission. Independent risk factors and infection prediction model were determined using Logistic regression analyses. Likelihood ratio test was used to detect the prediction effect of the model. Receiver Operating Characteristic curve and the corresponding area under the curve were used to measure the predictive accuracy of indicators for urinary tract infection. Results Of the 186 subjects, there were 35 cases of urinary tract infection. Elevated interleukin-6, higher NIHSS, and decreased hemoglobin may be used to predict urinary tract infection. And, the predictive model for urinary tract infection (including sex, NIHSS, interleukin-6, and hemoglobin) have the best predictive effect. Conclusion This study is the first to discover decreased hemoglobin which may predict urinary tract infection. The prediction model shows the best accuracy.

Background

Stroke has become the disease with the first disability and the second mortality rate in the world (1). Ischemic stroke accounts for 87% of all stroke patients (2). Stroke can cause immunosuppression and the transfer and ectopic of specific intestinal flora, which makes stroke patients more susceptible to be infected (3, 4). The concept of post-stroke infection (PSI) was first defined by Vargis (5) in 2006. After that, Emsley and Hopkrns (6) supplemented this concept which mainly referred to the infection that occurred 48 hours after the onset of stroke. In addition, the infection was not in its occurrence or incubation when a stroke occurred. PSI mainly includes stroke-associated pneumonia (SAP) and urinary tract infection (UTI). The probability of infection after stroke is about 25%-65% (7). And, SAP has a greater effect on prognosis than UTI (8). However, studies of SAP have been relatively mature. By summarizing a large number of previous studies, the predictors of SAP include multiple vertebrobasilar stroke, National Institutes of Health Stroke Scale score, mechanical ventilation, nasogastric tube use, and dysphagia (9). However, there are relatively few studies on urinary tract infections. The incidence of urinary tract infection is about 19% (10). In addition, the occurrence of infection can further aggravate the physical damage caused by stroke, and this process will form a vicious circle with stroke (11-16). The circle will lead to a worse clinical prognosis (7, 17-20).

Therefore, the prevention and treatment of post-stroke infection are particularly critical. In previous studies, preventive antibiotic therapy did not improve functional outcome in relatively unselected patients with stroke (21-24). On the contrary, actively searching for signs of infection and prophylactic use of antibiotics were beneficial for patients at high risk of infection (25-28). In 1997, Fassbender found that interleukin-6 (IL-6) might be feasible in the prediction of post-stroke infection, which was the earliest study on the prediction of post-stroke infection (29). In later studies, risk factors for post-stroke infection

had been found to include higher age, procalcitonin (PCT), interleukin-6, C-reactive protein (CRP), higher NIHSS (National Institute of Health stroke scale) score at admission, diabetes, etc (6, 30-32).

In this study, we attempted to identify early predictors and construct a prediction model which is simple and practical for urinary tract infection in patients with acute ischaemic stroke.

Methods

2.1. Patient Population

A total of 186 patients with acute ischemic stroke admitted to the stroke unit of the department of neurology of Shanghai Tenth People's Hospital from June 2014 to December 2016 were continuously collected. Patients were enrolled in the study if they (1) had an acute-onset focal neurological deficit combined with neuroimaging evidence of cerebral infarction by cranial computed tomography or magnetic resonance imaging, (2) were hospitalized within 48 hours after onset of stroke symptoms, (3) were not in the infection incubation or occurrence phase at the onset of stroke, (4) had no signs of infection within 48 hours after the onset of stroke, and (5) gave informed consent. Patients were excluded from the study if they (1) had an intracranial hemorrhage, hypoglycemia, or other causes of a new focal deficit, (2) had severe liver, kidney and heart dysfunctions, (3) were being treated with antibiotics, immunosuppressors or corticosteroids in the previous 3 months and significant disability before the index stroke, (4) had a history of surgery or trauma within a month, (5) had immunodeficiency or malignant tumors, and (6) had diseases of the blood system or serious lung diseases.

2.2 Clinical Management and Data.

The stroke patients were admitted to a dedicated stroke unit. The neurological course was assessed using the NIHSS score (33) and the OCSP (Oxfordshire Community Stroke Project) classification (34) by neurologists at admission. On the first day of hospitalization, clinical and demographic data of the patients, including age, sex and vascular risk factors (arterial hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, and smoking status) were recorded. Every patient's fasting venous blood was sampled on the second day of admission. The venous blood was used to examine laboratory indicators such as interleukin-6, procalcitonin, etc. In addition, all patients completed the examination of stroke and post-stroke infection after admission.

2.3 Outcome Measures

UTI was defined as a body temperature ($>38^{\circ}\text{C}$) with urinary tract symptoms and positive midstream urine culture results (growth of bacteria >105 colony forming units/mL and no more than two microbial species) (35). SAP was defined as fever ($>38^{\circ}\text{C}$) and/or leucopenia ($<4000 \times 10^9/\text{L}$ cells) or leukocytosis ($>12000 \times 10^9/\text{L}$ cells), and at least two of the following: (1) New onset of purulent sputum, change in the character of sputum, or increased respiratory secretions, or increased suctioning requirements; (2) New onset or worsening cough, or dyspnea, or tachypnea; (3) Rales, or bronchial breath sounds; 4. Worsening

gas exchange, increased oxygen requirements. In addition, SAP was diagnosed when additionally typical chest X-ray or computed tomography (CT) changes were present (35, 36). The diagnostic criteria for upper respiratory tract infection were flu-like symptoms and sinusitis (37). Other infections were diagnosed according to the diagnostic criteria for the corresponding diseases. After the infection was diagnosed, we divided the infected patients into urinary tract infection group, other infection type groups, and non-infected group.

2.4 Statistical Analysis

Data were sorted out and statistically analyzed using SPSS (Statistical Product and Service Solutions) software package version 22.0. Continuous variables that conformed to a normal distribution were expressed as means \pm standard deviations. If the continuous variables did not fit the normal distribution, they were represented by M ($Q25-Q75$). The two groups of continuous variables subject to normal distribution were compared by T test (Student's t test). Wilcoxon Signed Rank test was used for two groups of measurement data that did not conform to normal distribution. Differences in categorical data between groups were examined using Pearson's chi-squared test. Independent risk factors were determined using multivariate Logistic regression analyses. Infection prediction model was established by binary Logistic stepwise regression analyses. After that, Likelihood ratio test was used to detect the prediction effect of the model. Receiver Operating Characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to measure the predictive accuracy of indicators and the model for urinary tract infection. P (probability) <0.05 was considered statistically significant in all these tests.

Results

3.1 Baseline characteristics

A total of 186 patients were included in the study, including 127 males, accounting for 68.28%, and 59 females, accounting for 31.72%. Among the subjects, the oldest was 95 years old, the youngest was 30 years old, and the average age was 66.88 ± 11.87 years old. Of the 186 subjects in the study, 64 were infected. The incidence of post-stroke infection was 34.41%. Among the infections, there were 23 cases of pulmonary infection, accounting for 35.94%; 32 cases of urinary tract infections, accounting for 50.00%; 6 cases of other infections (5 cases of acute upper respiratory tract infection, 1 case of acute periodontitis), accounting for 9.38 %; 3 cases of pulmonary infection combined with urinary tract infection, accounting for 4.69%.

3.2 Urinary tract infection group

3.2.1 Indicators of patients with and without urinary tract infection group

A total of 35 cases of urinary tract infection occurred in 186 patients. The incidence rate was 18.82%. Comparison of indicators related to patients with and without urinary tract infection occurred in Table 1. Indicators that accounted for a higher proportion in the infected group than those in the uninfected group

included female, no smoking history, higher admission NIHSS score. In the laboratory test results, the levels of interleukin-6 and procalcitonin in patients with urinary tract infection were higher than those in patients without infection, and the levels of hemoglobin in patients with urinary tract infection were lower than patients without infection.

3.2.2 Independent influencing factors of UTI

Multivariate Logistic regression analysis showed that sex, smoking, NIHSS score, interleukin-6, and hemoglobin were independent influencing factors of urinary tract infection. And, if the NIHSS score and interleukin-6 levels were higher, the risk of infection was greater. However, if the levels of hemoglobin were higher, the risk of infection was lower. Smoking history was a protective factor of urinary tract infection. Conversely, female was a risk factor for urinary tract infection. (Table 2)

3.2.3 Establishment and analysis of UTI prediction model

The index with P-value less than 0.10 in the comparison between the infected patients and the non-infected patients was included in the logistic regression model, and the forward method was used to perform stepwise regression. The model standard was $P<0.05$, and the exclusion criterion was $P>0.10$. The variables that eventually entered the model were sex, NIHSS score, interleukin-6, and hemoglobin.(Table 3)

Then we assigned the variables that entered the regression model. The assignment table was shown in Table 4.

The variables that finally entered the model were sex (X_1), NIHSS score (X_2), interleukin-6 (X_3), and hemoglobin (X_4).

The regression model was: Logit (P) = $2.160X_1+0.303X_2+0.145X_3-0.049X_4$.

Next, the model was tested for likelihood ratio, and the test result showed that the regression model was statistically significant ($\chi^2=116.894$, $P<0.001$). The prediction of infection in the urinary tract infection prediction model showed that of the 35 patients with urinary tract infection, 17 were correctly predicted; 122 were patients with no infection, and 115 were correctly predicted. The accuracy of the regression model prediction was 85.4%.

3.2.4 Predictive diagnostic value of different indicators for UTI

Multivariate analysis had shown that NIHSS score, interleukin-6, and hemoglobin were independent influencing factors affecting urinary tract infection. The ROC analyses were performed on the NIHSS score, interleukin-6, procalcitonin, and urinary tract infection prediction model, as shown in Figures 1-4. The results showed that different predictors and the predictive model all could predict the occurrence of urinary tract infection ($P<0.05$). The area under the ROC curve of NIHSS score, interleukin-6, and hemoglobin for urinary tract infection was 0.711 (95% confidence interval: 0.607 to 0.815), 0.661 (95%

confidence interval: 0.546 to 0.777), and 0.625 (95% confidence interval: 0.510 to 0.740), respectively. Furthermore, NIHSS score at a cutoff value of 3.5 exhibited the best balance between sensitivity and specificity for detection of urinary tract infection, followed by interleukin-6 (cutoff value, 4.910 pg/ml) and hemoglobin (cutoff value: 123.50g/l). The area under the ROC curve of the predictive model of UTI was 0.890 (95% confidence interval: 0.832 to 0.948). When the probability of regression model $P \geq 0.2014$ was predicted to occur, the sensitivity at this time was 88.57%, and the specificity was 77.05%. (Table 5)

Discussion

4.1 Hemoglobin

This study is the first to discover that the decreased hemoglobin levels at admission may predict the occurrence of UTI. Hemoglobin is a protein responsible for carrying oxygen in an organism (38). Decreased hemoglobin content in the blood will result in a relative decrease in oxygen supply to the local tissues and organs, which may result in a decrease in the metabolism of tissues and organs, thereby facilitating secondary infection. The previous study has found that bacterial infections were associated with hemoglobin levels (39). Moreover, Eneroth's research has found that patients with anemia were prone to infection, suggesting that reduced hemoglobin might be a predictor of infection (40). In addition, Kotze's study has found that low-grade inflammation was inversely related to hemoglobin content, which meant that the lower the hemoglobin content, the higher the likelihood of an inflammatory response (41). The mechanism of this phenomenon may be that hemoglobin can naturally decompose in red blood cells, and then some larger fragments are generated and secreted into the blood. These fragments are further broken down into smaller fragments which form a "hemoglobin peptide library" in different tissues. The "hemoglobin peptide library" can produce different biological effects which include "antimicrobial hemoglobin-derived peptides". Then, the "antimicrobial hemoglobin-derived peptides" can produce antibacterial effects, thereby reducing inflammation caused by microbial infections (42).

4.2 Interleukin-6, NIHSS score, and Sex

Our study found that elevated levels of interleukin-6 and higher admission NIHSS score might be used as independent risk factors to predict UTI.

Interleukin-6 is a cytokine produced by monocytes, macrophages, lymphocytes, and so on, and belongs to the class of interleukins. It is an important mediator of the acute phase of inflammation. And, it will rise in the acute phase of inflammation (43). Bacterial infections can induce normal cells to produce interleukin-6. Subsequently, the interleukin-6 will stimulate the proliferation and differentiation of cells involved in the immune response, thereby enhancing the function of these cells. Finally, through this process, interleukin-6 plays an anti-infective role (44). The results of our study found that interleukin-6 might be used for the prediction of UTI after a stroke is about the same as previous studies(16, 17, 29).

The NIHSS score can assess the severity of a patient's stroke to some extent and can roughly predict the size of the stroke area (45). Previous research found that brain injury after an ischaemic stroke could lead

to immunosuppression (3) which had been related to the increased risk of infection after stroke (46). Moreover, the severity of stroke is a risk factor for post-stroke immunosuppression (47). And, a large number of studies have previously demonstrated that higher NIHSS score at admission could be used for post-stroke infection predictions (14, 32, 48-50). The results were about repeated in our trial.

Our study has found that female was an independent risk factor for urinary tract infections. The reason is caused by the particularity of the structure of the female genitourinary system. Women's urethra is shorter than men, which is more conducive to bacterial invasion. Moreover, the female urethra is close to the vagina and anus which contain a lot of bacteria. And, vaginal secretions are also a good medium for bacteria to multiply. These conditions can be used to explain that women are more likely to get a urinary tract infection. At the same time, previous research has reached the same conclusion (51).

4.3 Smoking

Interestingly, our study found that smoking history was a protective factor for urinary tract infection after ischemic stroke. The phenomenon of protective effects on smoking was first discovered in the field of heart disease. In coronary myocardial infarction, patients with a history of smoking had a lower incidence, mortality, and myocardial reinfarction rate than those without a history of smoking. The study also found that no smoking history was an independent risk factor for myocardial infarction recurrence (52). Moreover, after an acute myocardial infarction, smokers exhibited a better clinical outcome than patients who have never smoked. In addition, coronary angiography showed that the area of coronary artery lesions in smokers was smaller (53). However, the above study only evaluated the history of smoking at admission and did not conduct subsequent assessments. It is speculated that the sudden cessation of smoking after admission may be used to explain the phenomenon of lower recurrent myocardial infarction and a better prognosis in patients with a history of smoking (54, 55).

Later, some studies also found that smokers showed a better prognosis in acute myocardial infarction (56-58). Novo summarized previous studies and speculated that possible causes of good prognosis in hospitalized patients with acute myocardial infarction included: (1) younger and less associated disease; (2) higher pre-hospital mortality; (3) smoking was more likely to cause myocardial infarction caused by thrombosis, which made patients obtain a better thrombolytic effect; (4) smoking could cause a protective effect similar to ischemic preconditioning. Moreover, he described the phenomenon of ischemic preconditioning in his research. It referred to a transient ischemic stimulus which gave cardiomyocytes better tolerance to subsequent ischemic events. The protective effect of ischemic preconditioning depended on functional channels of gap junction intercellular communication, which were specialized intercellular contacts that allowed electrical impulse propagation among cardiomyocytes. The main structure of the gap junction was composed of connexin 43, which played a major role in ischemic preconditioning. In addition, smoking could induce gap junction remodeling of cardiomyocytes, thereby increasing the function of gap junctions. And, the enhanced function could better protect cells. This phenomenon might explain the better prognosis in patients with myocardial infarction who had a history of smoking (59).

Previous research found that gap junctions existed between cells of various tissues, except for blood cells and skeletal muscle cells. Moreover, they were widely present between urinary tract cells, bronchial epithelial cells, alveolar epithelial cells, alveolar macrophages, smooth muscle cells, and pulmonary artery endothelial cells. The gap junction could help the cilia to clear the mucus, facilitate the secretion of alveolar surfactant, and promote the synchronous contraction of pulmonary vascular smooth muscle cells. It could also fight the lung inflammation and may even have a therapeutic effect on lung inflammation (60). Besides, connexin 43 could increase pulmonary vascular permeability, which was more conducive to anti-inflammatory cells to fight infection (61). So we speculate that gap junctions in urinary tract cells may also exert anti-inflammatory effects in the same way.

Since previous studies have found that smoking had a protective effect on the damage caused by acute myocardial infarction, then we have reason to speculate that smoking may exert anti-inflammatory effects by inducing remodeling of gap junctions. Moreover, isoflurane pretreatment can reduce the release of proinflammatory factors in the lungs and the mortality caused by sepsis (62). Pretreatment with sevoflurane and isoflurane can reduce the body's inflammatory response and pneumonia damage caused by sepsis (63). Cigarette smoke contains alkane components. It is speculated that smoking may have a similar pretreatment effect. Smoking thus has a similar protective effect on ischemic stroke infection. Cigarette smoke can also increase the function of macrophages to fight the infection caused by Leishmania donovani (64). More importantly, stroke patients will suddenly quit smoking after admission, which may also be the reason why the probability of urinary tract infection in stroke patients with smoking history found in this study is low. Besides, it was found that among all stroke patients included in our study, the age of smokers was significantly lower than that of non-smokers ($P<0.05$). The immunity and general condition of younger people may be better than those of the elderly, and past diseases may be less, resulting in a lower risk of infection. This finding may also be the reason why smoking is a protective factor for infection after ischemic stroke.

This study has some limitations. First, the number of cases included in this study is not large enough, and the conclusions obtained may not fully reflect the overall situation. There may be bias. Second, this study did not include all characteristics reported in previous studies as possible risk factors for infection, such as interleukin-10, IL-1ra, etc. Third, this study did not further observe the guiding role of these predictive models for antibiotic prophylaxis. Subsequent studies should include larger samples and further observation of the clinical effect of the predictive model for prophylactic antibiotic use.

Conclusions

In summary, our study is the first to discover that the decreased hemoglobin levels at admission may predict the occurrence of UTI. Besides, elevated levels of interleukin-6 and higher NIHSS score at admission may also be used as independent risk factors to predict UTI. Moreover, the prediction model of UTI has the best predictive effect. And, the model which is simple and practical included risk factors for sex (female), higher NIHSS score, elevated interleukin-6 levels, and reduced hemoglobin levels. Therefore,

the conclusions of this study are important for improving the prognosis of patients with acute ischemic stroke. And, the results may provide a good reference for urinary tract infection after ischemic stroke.

Abbreviations

PSI: post-stroke infection

SAP: stroke-associated pneumonia

UTI: urinary tract infection

IL-6: interleukin-6

PCT: procalcitonin

CRP: C-reactive protein

NIHSS: National Institute of Health stroke scale

OCSP: Oxfordshire Community Stroke Project

SPSS: Statistical Product and Service Solutions

T test: Student's t test

ROC: Receiver Operating Characteristic

AUC: area under the curve

P: probability

TACI: total anterior circulation infarction

PACI: partial anterior circulation infarction

LACI: lacunar infarction

POCI: posterior circulation infarction

LDL: low density lipoprotein

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was got from the local Ethics Committee of Shanghai Tenth People's Hospital (SHDSYY-2014-135), Tongji University, Shanghai, China. This study was authorized by all patients or their legal representatives. And, written informed consent was obtained from all participants in this study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The datasets used during the current study are available from the corresponding author on reasonable request.

COMPETING INTERETS

None of the authors have any actual or potential conflict of interest.

FUNDING

This work was supported by the Jiading District Medical Key Specialist Construction Plans (No. JDYZDZK-5) which bears the cost of writing the manuscript and the National Natural Science Foundation of China (No. 81571033) which bears the design and implementation costs of the research.

AUTHORS' CONTRIBUTIONS

YL wrote the first draft of the manuscript and gathered data. YZ conceived the research and modified the manuscript. JX was involved in data analyses. All authors reviewed and edited the manuscript and approved the final version of the article.

ACKNOWLEDGMENTS

Not applicable.

References

1. Ye H, Wang L, Yang XK, Fan LP, Wang YG, Guo L. Serum S100B levels may be associated with cerebral infarction: a meta-analysis. *Journal of the neurological sciences*. 2015;348(1-2):81-8.
2. He S, Wang C, Dong H, Xia F, Zhou H, Jiang X, et al. Immune-related GTPase M (IRGM1) regulates neuronal autophagy in a mouse model of stroke. *Autophagy*. 2012;8(11):1621-7.
3. Shi K, Wood K, Shi FD, Wang X, Liu Q. Stroke-induced immunosuppression and poststroke infection. *Stroke & Vascular Neurology*. 2018;3(1):34-41.
4. Stanley D, Mason LJ, Mackin KE, Srikhanta YN, Lyras D, Prakash MD, et al. Translocation and dissemination of commensal bacteria in post-stroke infection. *Nature medicine*. 2016;22(11):1277-84.

5. Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, et al. Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials? *Stroke; a journal of cerebral circulation*. 2006;37(2):461-5.
6. Emsley HCA, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *The Lancet Neurology*. 2008;7(4):341-53.
7. Kwan J, Hand P. Infection after acute stroke is associated with poor short-term outcome. *Acta neurologica Scandinavica*. 2007;115(5):331-8.
8. Ulm L, Ohlraun S, Harms H, Hoffmann S, Klehmet J, Ebmeyer S, et al. STRoke Adverse outcome is associated WIth NoSocomial Infections (STRAWINSKI): procalcitonin ultrasensitive-guided antibacterial therapy in severe ischaemic stroke patients - rationale and protocol for a randomized controlled trial. *International journal of stroke : official journal of the International Stroke Society*. 2013;8(7):598-603.
9. Yuan MZ, Li F, Tian X, Wang W, Jia M, Wang XF, et al. Risk factors for lung infection in stroke patients: a meta-analysis of observational studies. *Expert review of anti-infective therapy*. 2015;13(10):1289-98.
10. Yan T, Liu C, Li Y, Xiao W, Li Y, Wang S. Prevalence and predictive factors of urinary tract infection among patients with stroke: A meta-analysis. *American journal of infection control*. 2017:S0196655317311422.
11. Shim R, Wong CHY. Ischemia, Immunosuppression and Infection—Tackling the Predicaments of Post-Stroke Complications. *International journal of molecular sciences*. 2016;17(1):64.
12. Klehmet J, Harms H, Richter M, Prass K, Volk HD, Dirnagl U, et al. Stroke-induced immunodepression and post-stroke infections: lessons from the preventive antibacterial therapy in stroke trial. *Neuroscience*. 2009;158(3):1184-93.
13. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Gomez-Choco M, et al. Catecholamines, infection, and death in acute ischemic stroke. *Journal of the neurological sciences*. 2007;252(1):29-35.
14. Worthmann H, Tryc AB, Dirks M, Schuppner R, Brand K, Klawonn F, et al. Lipopolysaccharide binding protein, interleukin-10, interleukin-6 and C-reactive protein blood levels in acute ischemic stroke patients with post-stroke infection. *Journal of neuroinflammation*. 2015;12:13.
15. Cowan LT, Alonso A, Pankow JS, Folsom AR, Rosamond WD, Gottesman RF, et al. Hospitalized Infection as a Trigger for Acute Ischemic Stroke: The Atherosclerosis Risk in Communities Study. *Stroke; a journal of cerebral circulation*. 2016;47(6):1612-7.
16. Wang H, Yan FL, Cunningham M, Deng QW, Zuo L, Xing FL, et al. Potential specific immunological indicators for stroke associated infection are partly modulated by sympathetic pathway activation. *Oncotarget*. 2016;7(32):52404-15.
17. Kwan J, Horsfield G, Bryant T, Gawne-Cain M, Durward G, Byrne CD, et al. IL-6 is a predictive biomarker for stroke associated infection and future mortality in the elderly after an ischemic stroke. *Experimental gerontology*. 2013;48(9):960-5.

18. Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. *European Journal of Neurology*. 2004;11(11):49-53.
19. Yousuf S, Atif F, Sayeed I, Wang J, Stein DG. Post-stroke infections exacerbate ischemic brain injury in middle-aged rats: immunomodulation and neuroprotection by progesterone. *Neuroscience*. 2013;239:92-102.
20. Miller CM, Behrouz R. Impact of Infection on Stroke Morbidity and Outcomes. *Current Neurology & Neuroscience Reports*. 2016;16(9):83.
21. Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, et al. The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial. *Stroke; a journal of cerebral circulation*. 2005;36(7):1495-500.
22. Kalra L, Irshad S, Hodsoll J, Simpson M, Gulliford M, Smithard D, et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet*. 2015;386(10006):1835-44.
23. Susann H, Odilo E, Christine RM, Susanne M, Ulrich D, Christian M, et al. Superiority of preventive antibiotic treatment compared with standard treatment of poststroke pneumonia in experimental stroke: a bed to bench approach. *Journal of Cerebral Blood Flow & Metabolism*. 2013;33(6):846-54.
24. Ormseth CH, Sheth KN, Saver JL, Fonarow GC, Schwamm LH. The American Heart Association's Get With the Guidelines (GWTG)-Stroke development and impact on stroke care. *Stroke & Vascular Neurology*. 2017;2(2):94-105.
25. Schwarz S, Al-Shajlawi F, Sick C, Meairs S, Hennerici MG. Effects of prophylactic antibiotic therapy with mezlocillin plus sulbactam on the incidence and height of fever after severe acute ischemic stroke: the Mannheim infection in stroke study (MISS). *Stroke; a journal of cerebral circulation*. 2008;39(4):1220-7.
26. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PloS one*. 2008;3(5):e2158.
27. Miller EC, Elkind MS. Infection and Stroke: an Update on Recent Progress. *Current neurology and neuroscience reports*. 2016;16(1):2.
28. European Stroke Organisation Executive C, Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular diseases*. 2008;25(5):457-507.
29. Fassbender K, Dempfle CE, Mielke O, Rossol S, Schneider S, Dollman M, et al. Proinflammatory cytokines: indicators of infection in high-risk patients. *Journal of Laboratory & Clinical Medicine*. 1997;130(5):535-9.
30. Hug A, Murle B, Dalpke A, Zorn M, Liesz A, Veltkamp R. Usefulness of serum procalcitonin levels for the early diagnosis of stroke-associated respiratory tract infections. *Neurocritical care*. 2011;14(3):416-22.

31. Zhang X, Wang F, Zhang Y, Ge Z. Risk factors for developing pneumonia in patients with diabetes mellitus following acute ischaemic stroke. *Journal of International Medical Research*. 2012;40(5):1860-5.
32. Friedant AJ, Gouse BM, Boehme AK, Siegler JE, Albright KC, Monlezun DJ, et al. A simple prediction score for developing a hospital-acquired infection after acute ischemic stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2015;24(3):680-6.
33. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. *NINDS TPA Stroke Study Group*. *Stroke; a journal of cerebral circulation*. 1994;25(11):2220-6.
34. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet (London, England)*. 1991;337(8756):1521-6.
35. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American journal of infection control*. 2008;36(5):309-32.
36. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. *Stroke; a journal of cerebral circulation*. 2015;46(8):2335-40.
37. Heikinheimo T, Broman J, Haapaniemi E, Kaste M, Tatlisumak T, Putala J. Preceding and poststroke infections in young adults with first-ever ischemic stroke: effect on short-term and long-term outcomes. *Stroke; a journal of cerebral circulation*. 2013;44(12):3331-7.
38. Lin T, Sammy F, Yang H, Thundivalappil S, Hellman J, Tracey KJ, et al. Identification of hemopexin as an anti-inflammatory factor that inhibits synergy of hemoglobin with HMGB1 in sterile and infectious inflammation. *Journal of immunology*. 2012;189(4):2017-22.
39. Pishchany G, McCoy AL, Torres VJ, Krause JC, Crowe JE, Jr., Fabry ME, et al. Specificity for human hemoglobin enhances *Staphylococcus aureus* infection. *Cell host & microbe*. 2010;8(6):544-50.
40. Eneroth H, Persson LA, El Arifeen S, Ekstrom EC. Infant anaemia is associated with infection, low birthweight and iron deficiency in rural Bangladesh. *Acta paediatrica (Oslo, Norway : 1992)*. 2011;100(2):220-5.
41. Kotze SR, Pedersen OB, Petersen MS, Sorensen E, Thorner LW, Sorensen CJ, et al. Low-grade inflammation is associated with lower haemoglobin levels in healthy individuals: results from the Danish blood donor study. *Vox sanguinis*. 2016;111(2):144-50.
42. Liepke C, Baxmann S, Heine C, Breithaupt N, Ständker L, Forssmann W-G. Human hemoglobin-derived peptides exhibit antimicrobial activity: a class of host defense peptides. *Journal of Chromatography B*. 2003;791(1-2):345-56.
43. Smith CJ, Emsley HC, Vail A, Georgiou RF, Rothwell NJ, Tyrrell PJ, et al. Variability of the systemic acute phase response after ischemic stroke. *Journal of the neurological sciences*. 2006;251(1-2):77-81.

44. Hartman J, Frishman WH. Inflammation and atherosclerosis: a review of the role of interleukin-6 in the development of atherosclerosis and the potential for targeted drug therapy. *Cardiology in review*. 2014;22(3):147-51.
45. Yaghi S, Herber C, Boehme AK, Andrews H, Willey JZ, Rostanski SK, et al. The Association between Diffusion MRI-Defined Infarct Volume and NIHSS Score in Patients with Minor Acute Stroke. *Journal of neuroimaging : official journal of the American Society of Neuroimaging*. 2017;27(4):388-91.
46. Ulrich D, Juliane K, Braun JS, Hendrik H, Christian M, Tjalf Z, et al. Stroke-induced immunodepression: experimental evidence and clinical relevance. *Stroke; a journal of cerebral circulation*. 2007;38(2 Suppl):770-3.
47. Andreas H, Alexander D, Nina W, Thomas G, Alexander L, Gerd A, et al. Infarct volume is a major determiner of post-stroke immune cell function and susceptibility to infection. *Stroke; a journal of cerebral circulation*. 2009;40(10):3226-32.
48. Tanzi P, Cain K, Kalil A, Zierath D, Savos A, Gee JM, et al. Post-stroke infection: a role for IL-1ra? *Neurocritical care*. 2011;14(2):244-52.
49. Wartenberg KE, Stoll A, Funk A, Meyer A, Schmidt JM, Berrouschot J. Infection after acute ischemic stroke: risk factors, biomarkers, and outcome. *Stroke research and treatment*. 2011;2011:830614.
50. Ashour W, Al-Anwar AD, Kamel AE, Aidaros MA. Predictors of early infection in cerebral ischemic stroke. *Journal of Medicine & Life*. 2016;9(2):163-9.
51. Flores-Mireles AL, Walker JN, Michael C, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*. 2015;13(5):269.
52. Mueller HS, Cohen LS, Braunwald E, Forman S, Feit F, Ross A, et al. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation*. 1992;85(4):1254.
53. Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J, et al. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. *Circulation*. 1993;87(1):53.
54. Kannel WB. Update on the role of cigarette smoking in coronary artery disease. *American heart journal*. 1981;101(3):319-28.
55. Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. *Lancet*. 1975;305(7904):415-20.
56. Kievit PC, Brouwer MA, Veen G, Aengevaeren WRM, Verheugt FWA. The smoker's paradox after successful fibrinolysis: reduced risk of reocclusion but no improved long-term cardiac outcome. *Journal of Thrombosis & Thrombolysis*. 2009;27(4):385.
57. Barua RS, Fridolin S, Sundararajan S, Grace H, Usman J, Cyrus B, et al. Acute cigarette smoke exposure reduces clot lysis–association between altered fibrin architecture and the response to t-PA. *Thrombosis Research*. 2010;126(5):426-30.

58. Aune E, Røislien J, Mathisen M, Thelle DS, Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. *Bmc Medicine*. 2011;9(1):97.
59. Novo R, Freire CM, Felisbino S, Minicucci MF, Azevedo PS, Zornoff LAM, et al. Smoking is Associated with Remodeling of Gap Junction in the Rat Heart: Smoker's Paradox Explanation? *Arquivos Brasileiros de Cardiologia*. 2013;100(3):274-80.
60. Wong P, Laxton V, Srivastava S, Chan YW, Tse G. The role of gap junctions in inflammatory and neoplastic disorders (Review). *Int J Mol Med*. 2017;39(3):498-506.
61. O'Donnell JJ, 3rd, Birukova AA, Beyer EC, Birukov KG. Gap junction protein connexin43 exacerbates lung vascular permeability. *PloS one*. 2014;9(6):e100931.
62. Qi Fang L, Ye Sen Z, Hong J, Hui X, Yu S. Isoflurane preconditioning ameliorates endotoxin-induced acute lung injury and mortality in rats. *Anesthesia & Analgesia*. 2009;109(5):1591.
63. Bedirli N, Demirtas CY, Akkaya T, Salman B, Alper M, Bedirli A, et al. Volatile anesthetic preconditioning attenuated sepsis induced lung inflammation. *Journal of Surgical Research*. 2012;178(1):e17-e23.
64. Maity PC, Bhattacharjee S, Majumdar S, Sil AK. Potentiation by cigarette smoke of macrophage function against Leishmania donovani infection. *Inflammation Research*. 2009;58(1):22-9.

Tables

Table 1 Univariate associations of factors influencing UTI.

	NO infection (n=122)	Urinary tract infection (n=35)	Statistics	p-value
Male sex/n (%)	100(82.0)	9(25.7)	$\chi^2=40.546$	<i>p</i> <0.001
Age, years	65.10±10.44	68.80±14.30	t=1.426	<i>p</i> =0.161
History				
Hypertension/n (%)	84(68.9)	28(80.0)	$\chi^2=1.653$	<i>p</i> =0.199
Diabetes mellitus/n (%)	46(37.7)	14(40.0)	$\chi^2=0.061$	<i>p</i> =0.805
Atrial fibrillation/n (%)	10(8.2)	6(17.1)	$\chi^2=2.378$	<i>p</i> =0.123
Smoker/n (%)	67(54.9)	2(5.7)	$\chi^2=26.730$	<i>p</i> <0.001
Assessment				
NIHSS score	3.0(1.0-4.0)	5.0(3.0-8.0)	Z=3.833	<i>p</i> <0.001
OCSP/n (%)				
TACI	1(0.8)	1(2.9)	$\chi^2=3.566$	<i>p</i> =0.312
PACI	39(32.0)	15(42.9)		
LACI	58(47.5)	11(31.4)		
POCI	24(19.7)	8(22.9)		
Laboratory indicators				
Interleukin-6 (pg/ml)	3.23	4.49	Z=2.925	<i>p</i> =0.003
Procalcitonin (ng/ml)	(2.00-4.49) 0.06	(2.53-11.00) 0.09	Z=2.445	<i>p</i> =0.014
Fasting glucose (m mol/l)	(0.03-0.10) 6.00	(0.05-0.15) 5.90	Z=0.168	<i>p</i> =0.867
C-reactive protein (mg/l)	(5.05-7.80) 3.40	(5.00-8.00) 3.40	Z=0.332	<i>p</i> =0.740
Glycosylated hemoglobin (%)	(3.40-4.56) 6.15	(3.27-6.20) 6.10	Z=0.314	<i>p</i> =0.753
LDL (m mol/l)	(5.60-8.05) 3.05	(5.80-7.50) 2.91	Z=0.441	<i>p</i> =0.659
Triglycerides (m mol/l)	(2.20-3.49) 1.37	(2.67-3.40) 1.34	Z=0.167	<i>p</i> =0.868
Total cholesterol (m mol/l)	(1.06-1.77) 4.61±1.06	(1.06-1.99) 4.75±0.66	t=0.884	<i>p</i> =0.379
Leukocyte count (*10 ⁹ /l)	6.62±1.57	7.36±2.32	t=1.781	<i>p</i> =0.082
Erythrocyte count (*10 ¹² /l)	4.61±0.68	4.36±0.52	t=1.963	<i>p</i> =0.051
Hemoglobin (g/l)	137.48±13.21	130.54±15.39	t=2.638	<i>p</i> =0.009

OCSP, Oxfordshire Community Stroke Project classification; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; LACI, lacunar infarction; POCI, posterior circulation infarction; LDL, low density lipoprotein.

Table 2 Multivariate Logistic regression analysis of factors influencing UTI.

	<i>B</i>	<i>S.E.</i>	<i>Wald</i>	<i>p-value</i>	<i>OR</i>	<i>95%CI</i>
Sex (female)	1.399	0.532	6.903	0.009	4.051	1.427-11.501
Smoker	-2.559	0.976	6.871	0.009	0.077	0.011-0.524
NIHSS score	0.331	0.096	11.938	0.001	1.392	1.154-1.680
Interleukin-6	0.161	0.081	3.953	0.047	1.175	1.002-1.377
Procalcitonin	0.800	2.279	0.123	0.726	2.225	0.026-193.600
Leukocyte count	0.071	0.166	0.183	0.669	1.074	0.775-1.486
Erythrocyte count	0.171	0.542	0.099	0.753	1.186	0.410-3.434
Hemoglobin	-0.047	0.022	4.427	0.035	0.954	0.913-0.997

Table 3 Logistic regression model results.

	<i>B</i>	<i>S.E.</i>	<i>Wald</i>	<i>p-value</i>	<i>OR</i>
Sex	2.160	0.477	20.475	0.000	8.671
NIHSS score	0.303	0.081	13.830	0.000	1.354
Interleukin-6	0.145	0.054	7.191	0.007	1.156
Hemoglobin	-0.049	0.008	37.419	0.000	0.953

Table 4 Variable assignments.

	Variable	Remarks
Sex	X ₁	1="male" 2="female"
NIHSS score	X ₂	-
Interleukin-6	X ₃	-
Hemoglobin	X ₄	-

Table 5 Predictive effects of different indicators on UTI.

	Cutoff	<i>AUC</i>	<i>95%CI</i>	<i>p-value</i>	Sensitivity	Specificity
NIHSS score	3.50	0.711	0.607-0.815	<0.001	68.57%	68.03%
Interleukin-6	4.910	0.661	0.546-0.777	0.004	48.57%	81.15%
Hemoglobin	123.50	0.625	0.510-0.740	0.025	87.70%	40.00%
Regression model	0.2014	0.890	0.832-0.948	<0.001	88.57%	77.05%

Figures

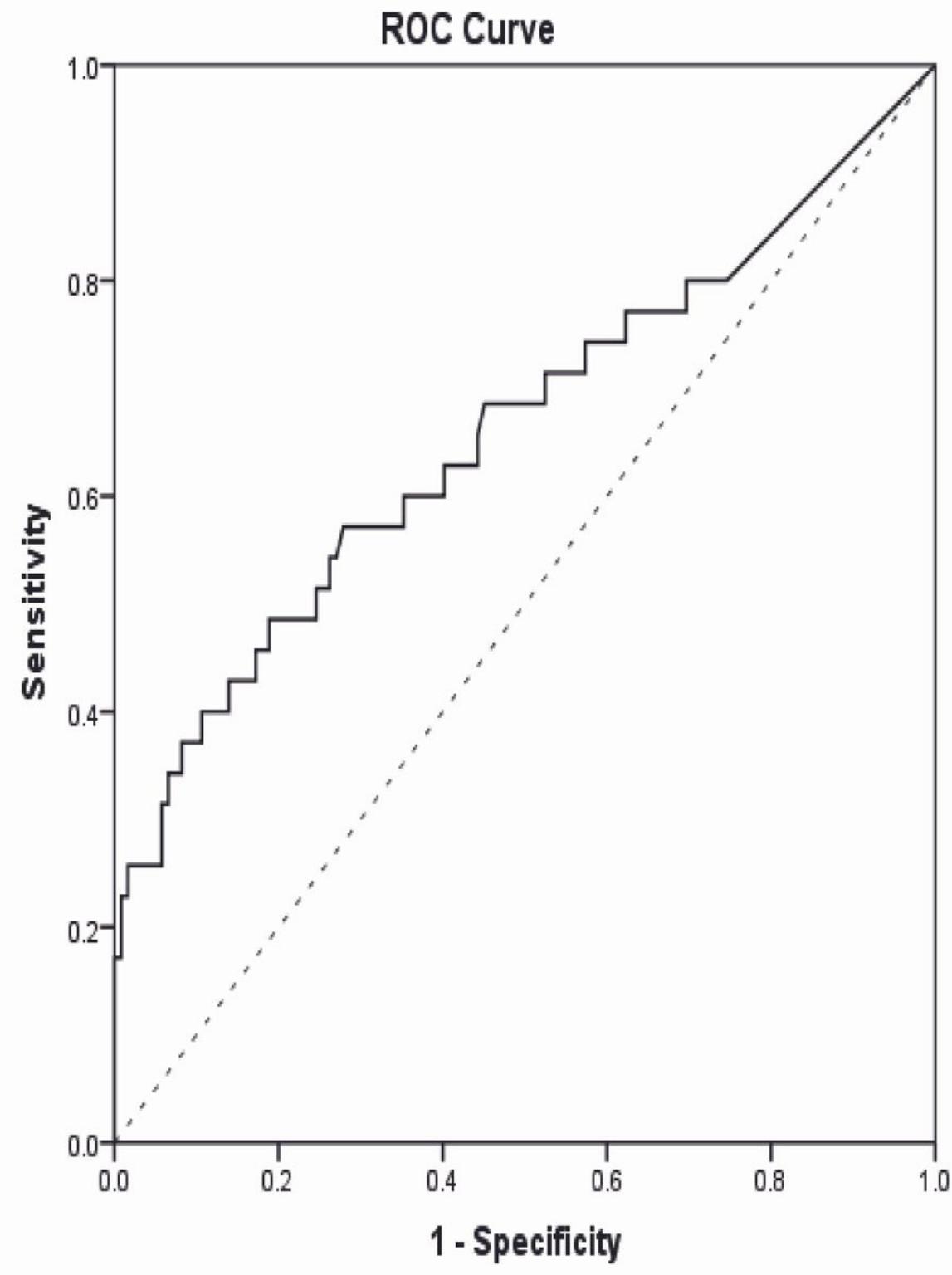


Figure 1

ROC curve of UTI with interleukin-6

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- YanxinZhaoFigure4.ROCcurveofUTIwithmodel.jpg
- YanxinZhaoFigure1.ROCcurveofUTIwithNIHSSscore.jpg
- YanxinZhaoFigure3.ROCcurveofUTIwithhemoglobin.jpg