DETERMINATION AND EVALUATION OF FACTORS ASSOCIATED WITH CATHETER-ASSOCIATED URINARY TRACT INFECTIONS AMONG ELDERLY NEUROSURGICAL PATIENTS

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Abstract. Catheter-associated urinary tract infections (CAUTI) are a cause of complications among neurosurgical patients, leading to greater morbidity and mortality. In this study, we aimed to determine and evaluate the factors significantly associated with CAUTI among elderly neurosurgical patients at the study institution in order to inform preventive measures and optimize patient care by identifying modifiable and non-modifiable factors associated with CAUTI. Inclusion criteria for study subjects were being a neurosurgical patient aged ≥60 years with an indwelling urinary catheter for ≥48 hours, having a negative urine culture on admission and in whom the complete medical records were available to review. Exclusion criteria were having abnormal coagulation testing, severe autoimmune disease or an endocrine disease. Subjects were divided into those with and without a CAUTI, and the final outcome, including death, was recorded. The criteria for a CAUTI were having a symptomatic urinary tract infection in a patient with an indwelling urinary catheter or developing an infection within 48 hours of catheter removal. This study was a retrospective review of patient charts. Multivariate logistic regression analysis was used to determine independent and dependent factors significantly associated with a CAUTI among study subjects. The following factors were significantly associated with a CAUTI on multivariate logistic regression analysis: a Glasgow Coma Scale (GCS) score <8 (adjusted odds ratio (aOR): 4.079, 95% confidence interval (CI): 1.156-14.393, $p = 0.029$), having diabetes mellitus (aOR: 2.822, 95% CI: 1.200-6.632, $p = 0.017$), having a urinary catheter for ≥7 days (aOR: 2.952, 95% CI: 1.115-7.810, $p = 0.029$), having a D-dimer level >0.5 mg/ml (aOR: 2.704, 95% CI: 1.146-6.381, $p = 0.023$), having undergone bladder irrigation (aOR: 3.179, 95%CI: 1.396-7.235, $p = 0.006$) and receiving ≥2 types of antibiotics during

hospitalization (aOR: 2.873, 95% CI: 1.247-6.620, $p = 0.013$). In summary, a number of factors were significantly associated with a CAUTI, some of which are modifiable. We conclude urinary catheters should be removed prior to 7 days where possible and bladder irritation should be avoided. Those with non-modifiable risk factors should be monitored regularly for a urinary tract infection. Further studies are needed to determine if making these modifications in this study population can reduce the incidence of CAUTI.

Keywords: geriatric, neurosurgery, urinary tract infection, associated factors, preventive measures

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INTRODUCTION

A catheter-associated urinary tract infection (CAUTI) is a symptomatic urinary tract infection occurring in a patient with an indwelling urinary catheter (Ma *et al*, 2022) or within 48 hours of catheter removal (Chenoweth *et al*, 2014; Liu *et al*, 2023a). A study from Shandong, China reported the incidence of a CAUTI to be 13.79 infections/1000 catheter days (Liu *et al*, 2023a). Another study from Qingdao, China reported the incidence of CAUTI to be 9.33% (Li *et al*, 2019). One study found the incidence of CAUTI was second only to pneumonia as a cause of hospital-acquired infections among elderly patients with urinary catheters (Wang *et al*, 2022).

Elderly neurosurgical patients may be frailer and may be more likely to have underlying chronic diseases

increasing their risk for developing CAUTI (Ma *et al*, 2023; Polites *et al*, 2014). A CAUTI can complicate the treatment of neurosurgical patients by increasing the risk for other infections, such as hemiparesis, meningitis and ventriculitis (Lin *et al*, 2022; Ellahi *et al*, 2021; Polites *et al*, 2014). These infections can lead to extended hospital stays, the need for additional surgical interventions, or delayed patient recovery from their neurological disease (Li *et al*, 2019; Shen *et al*, 2024; Wang *et al*, 2022). It is estimated that 65%-70% of CAUTI can be prevented by managing the duration of having a urinary catheter (Griffiths and Fernandez, 2007), having correct catheter hygiene (Yang *et al*, 2023), removing unnecessary catheters (Zhou *et al*, 2022), monitoring and managing diabetes (Yang *et al*, 2023) and using antimicrobial prophylaxis in specific high-risk cases, such as those involving immunocompromised elderly patients or patients undergoing prolonged catheterization due to complex neurosurgical interventions (Zhou *et al*, 2022).

During 2022, in the Department of Neurosurgery, Shanghai Tongren Hospital, PR of China, 711 out of a total of 2835 neurosurgical patients (25.1%) had a urinary catheter placed. Of these, 43 (6% of those with catheters) developed a CAUTI. Of those who developed a CAUTI, 38 (88%) were aged ≥60 years (Rabbani *et al*, 2022). The total number of days in which patients had urinary catheters was 3838 days, giving a CAUTI incidence of 11 cases/1000 catheter days for that year (Kumar *et al*, 2022).

One study reported the organisms causing CAUTI were: Gram-negative bacteria in 34%, Gram-positive bacteria in 46% and fungi in 20%; Enterococcus faecalis was the most common organism isolated (Chen *et al*, 2023). This information is important for guiding antimicrobial therapy. The presence of fungi in the above list highlights the importance of considering fungal pathogens as a cause of CAUTI (Chen *et al*, 2023). This data shows the necessity of ongoing surveillance and infection control measures to mitigate the risk of CAUTI.

Hemiparesis may be associated with CAUTI among neurosurgical patients (Gong *et al*, 2017). A previous study reported 52.6% of elderly patients with CAUTI had

hemiparesis. Prolonged immobility and poor bladder management have been reported to be associated with CAUTI (Gong *et al*, 2017). Elevated calcitoninogen and D-dimer levels have also been reported to be associated with CAUTI (Bailly, 2022).

Given the morbidity and mortality associated with CAUTI among elderly neurosurgical patients, we aimed to determine what modifiable and non-modifiable factors were associated with CAUTI at our institution during the study period in order to inform efforts to prevent CAUTI in this patient population.

MATERIALS AND METHODS

Study subjects

Inclusion criteria for study subjects were: neurosurgical patients, aged ≥60 years, having an indwelling urinary catheter for ≥48 hours, having a negative urine culture on admission and having complete medical records available for retrospective review.

Exclusion criteria for study subjects were: having abnormal coagulation testing, severe autoimmune disease or other significant endocrine diseases (excluding diabetes mellitus).

Evaluated factors

Factors studied for their association with CAUTI were: (1) patient-related factors, such as female gender, having diabetes mellitus, having hypertension, having an elevated D-dimer level , having an elevated c-reactive protein level, having an elevated calcitonin level, having leukocytosis, having hemiparesis, having pre-existing genitourinary abnormalities, and having a GCS score <8; (2) environmental factors, such as length of hospital stay ≥15 days, having an emergency admission, having undergone mechanical ventilation, ICU admission or tracheotomy; (3) medication-related factors, such as the use of ≥2 types of antibiotics; and (4) procedural factors, such as having undergone bladder flushing and the number of days a urinary catheter was left in place (Fig 1).

Data collection

The following data were collected from the medical records of each study subject: subject gender, history of diabetes mellitus, history of hypertension, D-dimer

level, c-reactive protein level, calcitoninogen level (elevated in cases of severe infection and organ failure), leukocyte count, history of stroke with hemiparesis, history of genitourinary disease, Glascow Coma Scale (GCS) score, length of hospital stay, mode of admission (admission through an emergency department or

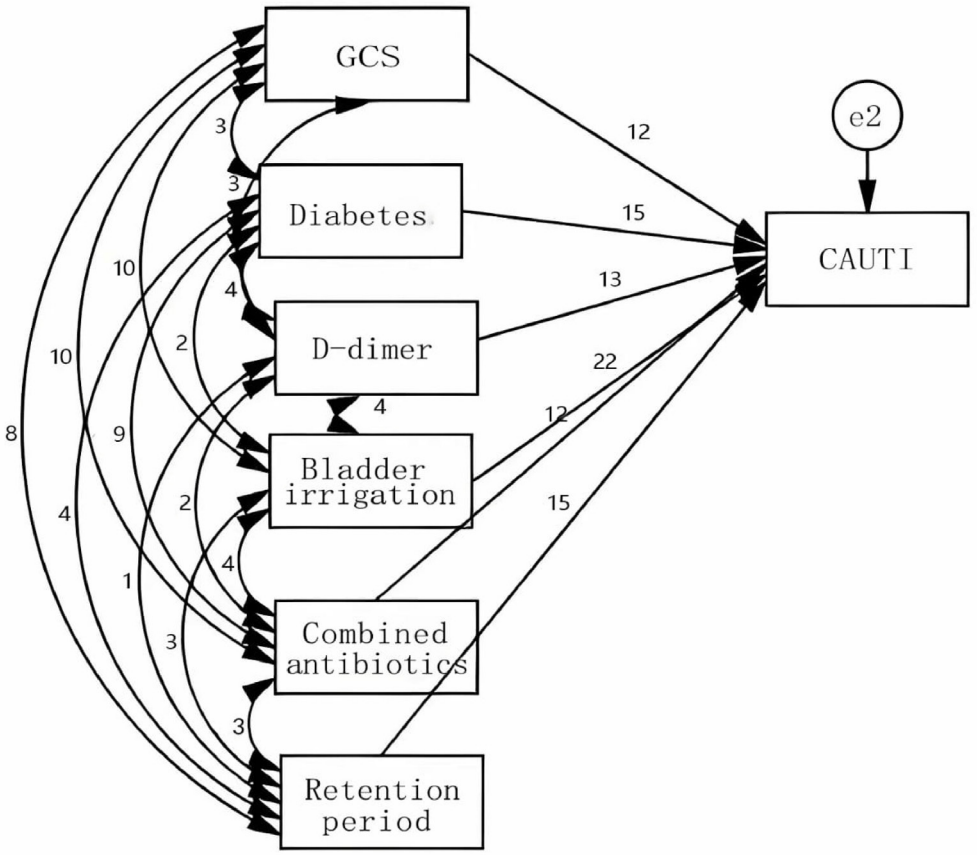

Fig 1 - Analysis of factors associated with CAUTI among study subjects

Note: The numbers in the figure represent the mutual influence between the associated factors as well as their influence on the occurrence of CAUTI, with larger numbers indicating greater influence.

CAUTI: Catheter-associated urinary tract infections; e2: Resulting event (a CAUTI) that occurs; GCS: Glasgow Coma Score

via a scheduled/planned route), mechanical ventilation during the hospitalization, tracheotomy, history of being admitted to the Intensive Care Unit (ICU), the number of antibiotics used in combination during the hospital stay, the number of days with a urinary catheter and whether the study subject underwent bladder irrigation therapy.

Statistical analysis

We performed univariate analysis to identify factors significantly associated with CAUTI using a *p*-value <0.05 for preliminary screening. Factors that were significant on univariate analysis were included in a multivariate logistic regression analysis model, where a *p*-value <0.05 was considered statistically significant.

We used the Chi-square test to assess potential associations between categorical variables and the occurrence of CAUTI on multivariate logistic regression analysis. The Statistical Package for the Social Sciences (SPSS), version 24.0 software (IBM, Armonk, NY) was used to conduct statistical calculations. A *p*-value <0.05 was considered statistically significant.

Odds ratios (OR) and 95% confidence intervals (CIs) were calculated to evaluate the strengths of associations between each factor and CAUTI.

Ethical consideration

This study was approved by the Medical Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Approval No: 727 Research No.023-Quick). Patient data were obtained without identifying factors so informed consent was not obtained to conduct this study.

RESULTS

Subject characteristics

A total of 242 subjects were included in the study, 143 males. The mean (±standard deviation) age of study subjects was 68 (±10) (range: 60-97) years. Sixty subjects (24.8%) had a craniocerebral injury, 74 (30.6%) had a stroke, 53 (21.9%) had a brain tumor, 50 (20.7%) had a cranial nerve disease and 5 (2.1%) had other neurological conditions. Of the total of 242 subjects, 38 (16%) had a CAUTI, 23 males. Ten subjects (26.3%) had a craniocerebral injury, 13 (34.2%) had a history of a stroke,

10 (26.3%) had a history of a brain tumor and 5 (13.2%) had a cranial nerve disease.

Univariate analysis of factors associated with CAUTI

On univariate analysis, the factors significantly associated with a CAUTI were: patient gender, a GCS score <8 points, having diabetes mellitus, having a urinary catheter for ≥7 days, a hospital stay of ≥15 days, emergency admission, D-dimer level >0.5mg/l, endotracheal intubation, admission to the ICU, having bladder washing and receiving ≥2 types of antibiotics were less than 0.05 (Table 1).

Multivariate logistic analysis of factors associated with CAUTI

The following factors were significantly associated with CAUTI on multivariate logistic regression analysis: a GCS score <8 (adjusted odds ratio (aOR): 4.079, 95% CI: 1.156-14.393, p = 0.029), diabetes mellitus (aOR: 2.822, 95% CI: 1.200-6.632, p = 0.017), having a urinary catheter for ≥7 days (aOR: 2.952, 95% CI: 1.115-7.810, p = 0.029), D-dimer level >0.5mg/l (aOR 2.704, 95% CI: 1.146-6.381), p = 0.023), bladder irrigation (aOR: 3.179, 95% CI: 1.396-7.235, p = 0.006), and receiving ≥2 types of antibiotics (aOR: 2.873, 95% CI: 1.247-6.620, p = 0.013) (Table 2).

DISCUSSION

In our study, a low GCS score was significantly associated with CAUTI. This is the same as the findings of a previous study from Anhui, China that reported a lower GCS was associated with prolonged catheterization increasing the risk of developing a CAUTI (Perrin *et al*, 2021). Patients with low GCS scores often have limited mobility and are fully dependent on nursing care for hygiene management. Inadequate or inconsistent hygiene care in such patients can increase the risk of catheter-associated infections, highlighting the importance of following nursing protocols to prevent CAUTI. Early removal of catheters in patients with impaired consciousness may reduce CAUTI rates (Kidd *et al*, 2015; Wang *et al*, 2022).

In our study, patients with DM were more likely to develop CAUTI, similar to the findings of previous studies (Kidd *et al*, 2015; Perrin *et al*, 2021). Hyperglycemia reduces the efficiency of neutrophils, reducing the body's ability to

Table 1

Univariate analysis of selected factor associations with CAUTI among study subjects

Relevant factor	Without CAUTI (N = 242)	With CAUTI (N = 38)	*p*-value
Sex, *n* (%)			0.020
Male	150 (62.0)	16 (42)	
Female	92 (38.0)	22 (58)	
Diabetes mellitus, *n* (%)			0.013
Yes	46 (19.0)	14 (37)	
No	196 (81.0)	24 (63)	
Hypertension, *n* (%)			0.202
Yes	126 (52.1)	24 (63)	
No	116 (47.9)	14 (37)	
Pre-existing Genitourinary system, *n* (%)			0.233
Abnormal	18 (7.4)	5 (1)	
Normal	224 (92.6)	33 (87)	
GCS score, *n* (%)			0.003
<8 points	75 (31.0)	3 (8)	
≥8 points	167 (69.0)	35 (92)	

Table 1 (cont)

Relevant factor	Without CAUTI (N = 242)	With CAUTI (N = 38)	*p*-value
Length of hospital stay in days, *n* (%)			0.017
<15	100 (41.3)	8 (21)	
≥15	142 (58.7)	30 (79)	
Duration of urinary catheter in days, *n* (%)			0.001
<7	114 (47.1)	7 (18)	
≥7	128 (52.9)	31 (82)	
Type of admission, *n* (%)			0.027
Emergency	119 (49.2)	26 (68)	
Non-emergency admissions	123 (50.8)	12 (32)	
Mechanical ventilation, *n* (%)			0.623
Yes	125 (51.7)	18 (47)	
No	117 (48.4)	20 (53)	
Admitted to ICU, *n* (%)			0.019
Yes	48 (19.8)	14 (37)	
No	194 (80.2)	24 (63)	
Tracheotomy, *n* (%)			0.191
Yes	17 (7.0)	5 (13)	
No	225 (93.0)	33 (87)	

Table 1 (cont)

Relevant factor	Without CAUTI (N = 242)	With CAUTI (N = 38)	*p*-value
Number of antibiotics, *n* (%)			0.006
<2	195 (80.6)	23 (61)	
≥2	47 (19.4)	15 (39)	
Bladder irrigation, *n* (%)			0
Yes	49 (20.3)	21 (55)	
No	193 (79.8)	17 (45)	
Hemiparesis, *n* (%)			0.096
Yes	54 (22.3)	4 (11)	
No	188 (77.7)	34 (89)	
Leukocyte count in the complete blood count, *n* (%)			0.496
$>9.5\times10^9$ cells/l	88 (36.4)	16 (42)	
3.5×10^9 - 9.5×10^9 cells/l	154 (63.6)	22 (58)	
c-reactive protein, *n* (%)			0.584
>10 mg/l	135 (55.8)	23 (61)	
≤10 mg/l	107 (44.2)	15 (39)	
Calcitoninogen, *n* (%)			0.521
>0.5 μg/l	109 (45.0)	15 (39)	
≤0.5 μg/l	133 (55.0)	23 (61)	

Table 1 (cont)

Relevant factor	Without CAUTI (N = 242)	With CAUTI (N = 38)	*p*-value
D-dimer, *n* (%)			0.012
>0.5 mg/l	110 (45.5)	9 (24)	
≤0.5 mg/l	132 (54.5)	29 (76)	

CAUTI: Catheter-associated urinary tract infections; GCS: Glasgow Coma Score; ICU: Intensive Care Unit; l: litre; mg/l: milligram per liter; µg/l: microgram per liter

Table 2

Multivariate logistic regression analysis selected factor associations with CAUTI among study subjects

Variant	*beta* value	Standard error	Vardø	Degrees of freedom	*p*-value	aOR	95% CI
GCS score	1.406	0.643	4.777	1	0.029	4.079	1.156-14.393
Diabetes	1.037	0.436	5.66	1	0.017	2.822	1.200-6.632
retention period	1.082	0.496	4.753	1	0.029	2.952	1.115-7.810
D-dimer	0.995	0.438	5.154	1	0.023	2.704	1.146-6.381
bladder irrigation	1.156	0.42	7.594	1	0.006	3.179	1.396-7.235
Combined antibiotics	1.055	0.426	6.142	1	0.013	2.873	1.247-6.620

aOR: adjusted odds ratio; CAUTI: Catheter-associated urinary tract infections; CI: confidence interval; GCS: Glasgow Coma Score

prevent infection (Fu *et al*, 2022). Poor glycemic control can cause glucosuria, increasing the chance of bacterial growth in the urinary tract (Fernandez and Griffiths, 2005). Diabetic patients often experience autonomic dysfunction, which may result in incomplete bladder emptying and increased residual urine, resulting in greater infection risk (Wang *et al*, 2022). The combination of these factors makes diabetic patients particularly susceptible to CAUTI. Close monitoring and effective management of blood glucose levels in patients with indwelling catheters may reduce infection risk (Perrin *et al*, 2021; Kidd *et al*, 2015). Our findings highlight the importance of maintaining proper glycemic control in catheterized elderly neurosurgical patients.

In our study, prolonged catheterization was significantly associated with CAUTI similar to previous studies (Perrin *et al*, 2021; Wang *et al*, 2022). Prolonged catheterization increases the chance of bacterial colonization. Longer categorization times allow bacteria to establish colonies and migrate along the catheter into the bladder, significantly increasing the risk of infection. Minimizing the duration of catheter use, should reduce the incidence of CAUTI.

In our study, we found a significant association between an elevated D-dimer level and CAUTI. A previous study reported D-dimer is an indicator of systemic inflammation (Griffiths and Fernandez, 2007). D-dimer is a non-specific inflammatory marker and may be elevated in urinary tract infections (Hur *et al*, 2019). A previous study (Wang *et al*, 2022) reported patients with an elevated D-dimer level were more likely to develop an infection; this may be because pro-inflammatory cytokines impaired immune responses and endothelial integrity, facilitating bacterial invasion.

In our study, receiving more than one type of antibiotic was significantly associated with CAUTI, similar to the results of a previous study (Perrin *et al*, 2021). The use of multiple antibiotics may disrupt the normal bacterial flora in the urinary tract, making it more susceptible to colonization by pathogens. Broad-spectrum antibiotics may alter the immune response in the elderly, increasing the risk for CAUTI (Kidd *et al*, 2015;

Wang *et al*, 2022). Further studies are needed to determine whether tailored antibiotic regimens, based on culture results and specific patient conditions, may help minimize CAUTI.

Limitations of this study

A limitation of this study was that it was conducted in only one hospital, we also had a small number of study subjects. Future studies need to include multiple hospitals to identify factors associated with CAUTI so the results may be applied to a larger population.

In summary, a number of factors were significantly associated with a CAUTI, some of which are modifiable. We conclude urinary catheters should be removed prior to 7 days where possible and bladder irritation should be avoided. Those with non-modifiable risk factors should be monitored regularly for a urinary tract infection. Further studies are needed to determine if making these modifications in this study population can reduce the incidence of CAUTI.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

Bailly C. Forsythosides as essential components of Forsythia-based traditional Chinese medicines used to treat inflammatory diseases and COVID-19. *World J Tradit Chin Med* 2022; 8(1): 1-20.

Chen L, Ma Y, Ma X, *et al*. TFEB regulates cellular labile iron and prevents ferroptosis in a TfR1-dependent manner. *Free Radic Biol Med* 2023; 208: 445-7.

Chenoweth CE, Gould CV, Saint S. Diagnosis, management, and prevention of catheter-associated urinary tract infections. *Infect Dis Clin North Am* 2014; 28(1): 105-19.

Ellahi A, Stewart F, Kidd EA, Griffiths R, Fernandez R, Omar MI. Strategies for the removal of short-term indwelling urethral catheters in adults. *Cochrane Database Syst Rev* 2021; 6(6): CD004011.

Fernandez RS, Griffiths RD. Clamping short-term indwelling catheters: a systematic review of the evidence. *J Wound Ostomy Continence Nurs* 2005; 32(5): 329-36.

Fu L, Ramos-Roman MA, Deng Y. Metabolic adaptation in lactation: insulin-dependent and -independent glycemic control. *J Transl Intern Med* 2022; 10(3): 191-6.

Gong Y, Zhao L, Wang L, Wang F. The effect of clamping the indwelling

urinary catheter before removal in cervical cancer patients after radical hysterectomy. *J Clin Nurs* 2017; 26(7-8): 1131-6.

Griffiths R, Fernandez R. Strategies for the removal of short-term indwelling urethral catheters in adults. *Cochrane Database Syst Rev* 2007; 2007(2): CD004011.

Hur EY, Jin Y, Jin T, Lee SM. Development and evaluation of the automated risk assessment system for catheter-associated urinary tract infection. *Comput Inform Nurs* 2019; 37(9): 463-72.

Kidd EA, Stewart F, Kassis NC, Hom E, Omar MI. Urethral (indwelling or intermittent) or suprapubic routes for short-term catheterisation in hospitalised adults. *Cochrane Database Syst Rev* 2015; 2015(12): CD004203.

Kumar V, Kaur N, Wadhwa P. Clinical evidence on the effects of saffron (*Crocus sativus* L.) in anxiety and depression. *World J Tradit Chin Med* 2022; 8(2): 181-7.

Li F, Song M, Xu L, Deng B, Zhu S, Li X. Risk factors for catheter-associated urinary tract infection among hospitalised patients: a systematic review and meta- analysis of observational studies. *J Adv Nurs* 2019; 75(3): 517-27.

Ma S, Gu J, Fan X. Need to clamp indwelling urinary catheters before removal after different durations: a systematic review and meta-analysis. *BMJ Open* 2023; 13(2): e064075.

Lin LQ, Wu BX, Lin MY, Chen QX, Xu DP. Interim analysis report of kuanxiong aerosol in improving angina and quality of life after percutaneous coronary intervention. *World J Tradit Chin Med* 2022; 8(1): 87-91.

Liu H, Li B, Xi P, *et al*. Time-varying functional connectivity of rat brain during bipedal walking on unexpected terrain. *Cyborg Bionic Syst* 2023a; 4: 0017.

Ma JY, Cruz J, Jin J, Peng XY, Zhang AM, Cheng XD. Therapeutics of integrative medicine ameliorate immunological disorders of the nervous system: a meta-analysis. *World J Tradit Chin Med* 2022; 8(1): 153-67.

Perrin K, Vats A, Qureshi A, *et al*. Catheter-associated urinary tract infection (CAUTI) in the NeuroICU: identification of risk factors and time-to- CAUTI using a case-control design. *Neurocrit Care* 2021; 34(1): 271-8.

Polites SF, Habermann EB, Thomsen KM, *et al*. Urinary tract infection in elderly trauma patients: review of the Trauma Quality Improvement

Program identifies the population at risk. *J Trauma Acute Care Surg* 2014; 77(6): 952-9.

Rabbani F, Yazdiniapour Z, Ghanadian M, Zolfaghari B, Maleki M, Shafiee F. Cytotoxicity and apoptosis assay of novel cyclomyrsinol diterpenes against breast cancer cell lines. *World J Tradit Chin Med* 2022; 8(2): 273-7.

Shen QQ, Jv XH, Ma XZ, *et al*. Cell senescence induced by toxic interaction between α-synuclein and iron precedes nigral dopaminergic neuron loss in a mouse model of Parkinson's disease. *Acta Pharmacol Sin* 2024; 45(2): 268-81.

Wang H, Shang Y, Wang E, *et al*. MST1 mediates neuronal loss and cognitive deficits: A novel therapeutic target for Alzheimer's disease. *Prog Neurobiol* 2022; 214: 102280.

Yang W, Ding N, Luo R, *et al*. Exosomes from young healthy human plasma promote functional recovery from intracerebral hemorrhage via counteracting ferroptotic injury. *Bioact Mater* 2023; 27: 1-14.

Zhou Y, Li Q, Pan R, *et al*. Regulatory roles of three miRNAs on allergen mRNA expression in *Tyrophagus putrescentiae*. *Allergy* 2022; 77(2): 469-82.