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Pyelonephritis due to *Escherichia coli* in the older population in Japan: Impacts on activities of daily living and medical costs

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Abstract: This study aimed to investigate differences in Activities of Daily Living (ADL), at admission and discharge, as well as the medical costs of pyelonephritis in older adults in Japan. Patients hospitalized for pyelonephritis between January 1, 2013 and March 31, 2019, were retrospectively enrolled. The inclusion criteria were urine culture within 48 h of admission with > 10^4 colony-forming units/mL of *Escherichia coli* and symptoms of pyelonephritis. Patients were divided into Young (20–64 years), Pre-old (65–74 years), Old (75–84 years), and Super-old (≥ 85 years). ADL and medical costs were compared. Finally, 393 patients were included: 112 (28.5%) were Young, 72 (18.3%) were Pre-old, 130 (33.1 %) were Old, and 79 (20.1%) were Super-old between January 1, 2013, and March 31, 2019. The median differences between Barthel Index (BI) scores, which indicates ADL, at admission and discharge were 0, 0, 25, and 23 in each age group, respectively ($p < 0.001$). No significant differences existed between the groups aged ≥ 65. Median medical costs were $3,368, $4,894, $5,372, and $6,078 for each age group, respectively ($p < 0.001$). Medical costs per day did not differ significantly between the groups ($p = 0.163$). Pyelonephritis due to *E. coli* in patients aged ≥ 75 is associated with a decline in ADL, longer hospital stays, and higher medical costs compared to that in young patients. Pre-old patients did not have lower ADL; however, they tended to have longer hospital stays and higher medical costs.

***Keywords*:** ageing, urinary tract infections, cost analysis

Introduction

Japan has a rapidly aging population. In 2021, 28.9% of the total Japanese population will be 65 years old or older, and 14.9% will be 75 years old or older (*1*). Urinary tract infections (UTIs) such as acute pyelonephritis are the second most common type of infection requiring hospitalization after lower respiratory tract infections (*2*). Complications and deaths from acute pyelonephritis are a significant medical burden, with the direct and indirect costs of acute pyelonephritis in the United States estimated at $2.14 billion in 2000 (*3*). In a retrospective study using surveillance data of hospitalized patients with UTIs in Japan (*4*), the average medical costs during hospitalization for treatment of UTIs were $4,250 (1 United States Dollar (USD) = 100 yen). The medical costs incurred by older adults were greater, with mean costs amounting to $3,154 for those ≤ 65 years and $4,630 for those aged ≥ 65 (*4*).

It has been reported that hospitalization due to acute illness is stressful for older adults and leads to a decline in physical functions (*5*). Even after the disease is cured, physical function often declines before hospitalization. As a result, the coordination of hospital transfers is difficult, leading to prolonged hospital stays, increased medical costs, and the development of new healthcare-associated infections.

Previous studies have reported low mortality due to pyelonephritis (*4*). Nonetheless, pyelonephritis still imposes a burden on the older population. Thus, it is necessary to examine the impact of pyelonephritis on physical function and medical costs, rather than on mortality. This study investigated the impact of pyelonephritis on physical function in older adults and the economy by comparing the Barthel Index (BI), which indicates Activities of Daily Living (ADL), with the medical costs of patients hospitalized for pyelonephritis.

Material and Methods

Study design

This retrospective observational single-center study was conducted at the National Center for Global Health and Medicine (NCGM) in Tokyo, Japan. The study protocol was reviewed and approved by the Ethics Committee of the Center Hospital of NCGM (NCGM-G-004104-02).

The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients

We enrolled patients with pyelonephritis who were hospitalized between January 1, 2013, and March 31, 2019. Patients who met the following clinical criteria were enrolled: *i*) Urine culture examination in the outpatient setting or within 48 h of admission demonstrating over 10^4 colony-forming units/mL of *Escherichia coli*, and *ii*) patients with at least one of the following: fever ≥ 38°C, costovertebral angle tenderness, suprapubic tenderness, urinary frequency, urinary urgency, and dysuria at the time of admission. The exclusion criteria were as follows: *i*) patients transferred from other hospitals, medical care facilities, or nursing homes; *ii*) patients with indwelling bladder catheters inserted at admission; *iii*) patients certified for Japanese long-term care insurance need levels over 3 (BI score < 60) (*6*) because their capacity for ADL declined before developing pyelonephritis, and *iv*) two or more hospitalizations for pyelonephritis during the study period. Enrolled patients were divided into four groups according to age: Young (20–64 years), Pre-old (65–74 years), Old (75–84 years), and Super-old (≥ 85 years). Data were collected by a single infectious disease doctor using an electronic medical chart.

Data

We collected the following data: age, sex, main department, underlying diseases and status of immunity, vital signs, quick Sequential Organ Failure Assessment (qSOFA), antibiotic treatment and invasive treatments, rehabilitation during hospitalization, medications used during hospitalization, admission to the intensive care unit, complications during hospitalization, *E. coli* bacteremia, extended-spectrum β-lactamase (ESBL)-producing *E. coli*, BI score at the time of admission and discharge, medical costs (1 USD = 140 yen), length of hospital stay, mortality during hospitalization, and discharge destination. We calculated the Charlson Comorbidity Index (CCI) scores (*7,8*). We also calculated qSOFA as a measure of severity (range, 0–3 points, with 1 point each for systolic hypotension [≤ 100 mmHg], tachypnea [≥ 22 /min], or altered mentation) (*9*). Antibiotic treatment included inappropriate empirical therapy, length of intravenous antimicrobial infusion, and rate of conversion to oral antibiotic therapy. Inappropriate empirical therapy was defined as the use of antibiotic agents against which the isolated *E. coli* was resistant. Invasive treatments include surgeries used to treat pyelonephritis, such as ureteral stent insertion, renal or bladder fistulotomy, percutaneous drainage, and open surgery. Complications during hospitalization included iatrogenic infections, peripheral line-associated bloodstream infection (PLABSI), central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and *Clostridioides difficile* infection (CDI). ESBL-producing *E. coli* were identified using the broth microdilution method, disk diffusion test, or Cica-beta test (Kanto Chemical, Tokyo, Japan).

The BI scale used in this study consists of 10 items: eating, bathing, grooming, dressing, defecation, urination, toilet use, movement, mobility, and stair climbing. Each item was scored as 0, 5, 10, or 15 points (*10*), with the maximum score varying per item and total scores ranging from 0 (complete dependence) to 100 (complete independence). Differences between the BI on admission and discharge were expressed as absolute values. Patients who died during hospitalization were excluded from the analysis. Medical costs were estimated without using a diagnosis-procedure combination (DPC). The discharge destinations included homes, other hospitals, and nursing homes.

Statistical analysis

Patient information was used to compare each group using Fisher's exact test and the Kruskal–Wallis test. The Bonferroni corrected p-value < 0.05 was deemed to be statistically significant. Categorical variables are presented as counts (%), and continuous variables are presented as median and interquartile range (IQR). All statistical analyses were performed using the EZR ver. 1.55 (*11*).

Results

Patients' characteristics

A total of 393 patients were included: 112 (28.5%) Young, 72 (18.3%) Pre-old, 130 (33.1%) Old, and 79 (20.1%) Super-old patients.

The patients' characteristics are shown in Table 1. Moreover, there were more female patients than male patients in all age groups. The percentage of patients with a CCI of 4 or higher increased with age; in the Super-old group, all patients had a CCI of 4 or higher. The rates of *E. coli* bacteremia in the Pre-old and Old groups were higher (61.1% and 60.0%, respectively) than those in the Young and Super-old groups (37.5% and 41.8%, respectively). The percentage of ESBL-producing *E. coli* was lower in the Super-old group (5.06%); however, it remained the same in the other groups (11.6–16.9%). The rates of inappropriate empirical therapy were 8 (7.1%), 4 (5.6%), 15 (11.5%), and 4 (5.1%) in Young, Pre-old, Old, and Super-old, respectively (p = 0.325). The rate of conversion to oral antibiotic therapy decreased with increasing age: 88 (78.6%), 36 (50.0%), 56 (43.1%), and 24 (30.4%) in Young, Pre-old, Old, and Super-old, respectively (p < 0.001). The length of intravenous

Table 1. Patients' characteristics, *n* (%)

Characteristics	Young n = 112	Pre-old n = 72	Old n = 130	Super-old n = 79	p-value*
Sex					
Female	89 (79.5)	48 (66.7)	90 (69.2)	60 (75.9)	0.200
Main department					0.971
Internal Medicine	81 (72.3)	53 (73.6)	94 (72.3)	59 (74.7)	
Urology	10 (8.9)	7 (9.7)	12 (9.2)	4 (5.1)	
Emergency department	11 (9.8)	9 (12.5)	22 (16.9)	15 (19.0)	
Others	10 (8.9)	3 (4.2)	2 (1.5)	1 (1.3)	
Charlson Comorbidities Index [IQR]	0 [0, 6]	3 [0, 4]	4 [3, 7]	6 [4, 8]	< 0.001
Myocardial infarction	1 (0.9)	5 (6.9)	18 (13.8)	8 (10.1)	< 0.001
Chronic heart failure	0 (0)	3 (4.2)	10 (7.7)	7 (8.9)	< 0.001
Stroke	3 (2.7)	5 (6.9)	20 (15.4)	13 (16.5)	< 0.001
Dementia	0 (0)	0 (0)	16 (12.3)	21 (26.6)	< 0.001
Chronic lung disease	3 (2.7)	5 (6.9)	7 (5.4)	3 (3.8)	0.536
Collagen disease	8 (7.1)	10 (13.9)	13 (10.0)	5 (6.3)	0.355
Severe renal dysfunction	1 (0.9)	5 (6.9)	9 (6.9)	4 (5.1)	0.074
Severe liver disease	0 (0)	1 (1.4)	1 (0.8)	1 (1.3)	0.697
Severe diabetes mellitus	3 (2.7)	7 (9.7)	3 (2.3)	1 (1.3)	0.039
Solid tumor	7 (6.3)	11 (15.3)	23 (17.7)	19 (24.1)	< 0.001
qSOFA[†]score	n = 76[‡]	n = 57[‡]	n = 110[‡]	n = 67[‡]	< 0.001
0	38 (50.0)	31 (54.4)	36 (32.7)	21 (31.3)	
1	31 (40.8)	14 (24.6)	61 (55.5)	35 (52.2)	
2	7 (9.2)	11 (19.3)	12 (10.9)	9 (13.4)	
3	0 (0)	1 (1.8)	1 (0.9)	2 (3.0)	
Immunodeficiency					
Human immunodeficiency virus infection	5 (4.5)	2 (2.8)	1 (0.8)	1 (1.27)	0.238
Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	
Steroid use	2 (1.8)	0 (0)	1 (0.8)	1 (1.3)	0.678
Chemotherapy	18 (16.1)	6 (8.3)	7 (5.4)	4 (5.1)	0.344
Immunosuppressed	19 (17.0)	5 (6.9)	5 (3.8)	5 (6.3)	0.762
Organ transplantation	0 (0)	0 (0)	0 (0)	0 (0)	
Rate of inappropriate empirical therapy	8 (7.1)	4 (5.6)	15 (11.5)	4 (5.1)	0.325
Length of intravenous antimicrobial infusion, days [IQR]	7 [5, 11]	9 [4, 14]	10 [7, 14]	11 [7, 14]	< 0.001
Rate of conversion to oral antibiotic therapy	88 (78.6)	36 (50.0)	56 (43.1)	24 (30.4)	< 0.001
penicillin	15 (17.0)	1 (2.8)	6 (10.7)	4 (16.7)	
penicillin/β-lactamase inhibitor	6 (6.8)	7 (19.4)	8 (14.3)	1 (4.2)	
cephalosporin	30 (34.1)	8 (22.2)	18 (32.1)	9 (37.5)	
fluoroquinolone	37 (42.0)	19 (52.8)	23 (41.1)	9 (37.5)	
sulfamethoxazole-trimethoprim	0 (0)	0 (0)	0 (0)	1 (4.2)	
tetracycline	0 (0)	1 (2.8)	1 (1.8)	0 (0)	
others	0 (0)	1 (2.8)	0 (0)	0 (0)	
Invasive treatment					0.341
Ureteral stent	10 (8.9)	5 (6.9)	8 (6.2)	2 (2.5)	
Renal fistula	0 (0)	0 (0)	0 (0)	0 (0)	
Bladder fistula	0 (0)	0 (0)	0 (0)	0 (0)	
Percutaneous drainage	0 (0)	2 (2.8)	0 (0)	1 (1.3)	
Open surgery	0 (0)	0 (0)	0 (0)	0 (0)	
Admission to the intensive care unit	6 (5.4)	7 (9.7)	11 (8.5)	11 (13.9)	0.232
Conducting rehabilitation during hospitalization	4 (3.6)	16 (22.2)	52 (40.0)	50 (63.3)	< 0.001
Complications during hospitalization					
Peripheral line-associated blood stream infection	1 (0.9)	0 (0)	1 (0.8)	0 (0)	
Central line-associated blood stream infection	1 (0.9)	0 (0)	0 (0)	0 (0)	
Catheter-associated urinary tract infection	0 (0)	1 (1.4)	0 (0)	0 (0)	
Clostridioides difficile infection	2 (1.8)	1 (1.4)	0 (0)	1 (1.3)	
Escherichia coli bacteremia	42 (37.5)	44 (61.1)	78 (60.0)	33 (41.8)	< 0.001
Extended-spectrum β-lactamase *Escherichia coli*	13 (11.6)	11 (15.3)	22 (16.9)	4 (5.1)	0.0600

*p-value is calculated for the difference among four groups. [†]qSOFA: quick Sequential Organ Failure Assessment. [‡]Patients without recorded respiratory rate, blood pressure, or mental status in their medical charts were excluded.

antimicrobial infusion and the rate of rehabilitation increased with age by 7, 9, 10, and 11 days, and 4 (3.6%), 16 (22.2%), 52 (40.0%), and 50 (63.3%) days in Young, Pre-old, Old, and Super-old patients, respectively (p < 0.001).

Outcomes

The patient outcomes are shown in Table 2. The median number of days of hospitalization was 8, 14, 14, and 16 days; the differences in BI between admission and

Table 2. Patients' outcomes

Variables	Young n = 112	Pre-old n = 72	Old n = 130	Super-old n = 79	p-value*
Barthel index at admission [IQR]	100 [100, 100]	100 [38 100]	50 [5, 100]	20 [0, 58]	< 0.001
Barthel index at discharge [IQR]	100 [100, 100]	100 [100, 100]	90 [60, 100]	58 [30, 100]	< 0.001
Differences in Barthel index between admission and discharge [IQR]	0 [0, 0]	0 [0, 45]	25 [0, 50]	23 [5, 49]	< 0.001
Medical costs, United States Dollar† [IQR]	$3,368 [2,886, 5,705]	$4,894 [4,019, 8,852]	$5,372 [4,575, 10,239]	$6,078 [5,169, 12,336]	< 0.001
Length of hospital stay, excluding death, days [IQR]	8 [6, 12]	14 [10, 18]	14 [10, 18]	16 [12, 21]	< 0.001
Medical costs per day of hospitalization, USD† [IQR]	$344 [321, 503]	$320 [301, 524]	$354 [320, 655]	$366 [324, 625]	0.163
Mortality during hospitalization, n (%)	1 (0.9)	2 (2.8)	5 (3.8)	1 (1.3)	0.392
14-day mortality, n (%)	1 (0.9)	1 (1.4)	4 (3.1)	1 (1.3)	0.176
30-day mortality, n (%)	0 (0)	2 (2.8)	4 (3.1)	1 (1.3)	0.146
Discharge destination, n (%)					< 0.001
Home	110 (99.1)	68 (97.1)	109 (87.2)	60 (76.9)	
Other hospitals	1 (0.9)	1 (1.4)	13 (10.4)	16 (20.5)	
Nursing home	0 (0)	1 (1.4)	3 (2.4)	2 (2.6)	

*p-value is calculated for the difference among four groups. Patient information was used to compare each group using Fisher's exact test and the Kruskal–Wallis test. The Bonferroni corrected p-value < 0.05 was deemed to be statistically significant. †1 United States Dollar = 140 yen

discharge were 0, 0, 25, and 23 in Young, Pre-old, Old, and Super-old patients, respectively ($p < 0.001$). The BI at admission and discharge was 100 in the Young and Pre-old groups, 50 and 90 in the Old group, and 20 and 58 in the Super-old group, respectively. The median medical costs (1 USD = 140 yen) were $3,368, $4,894, $5,372, and $6,078 in the Young, Pre-old, Old, and Super-old groups, respectively ($p < 0.001$). Nevertheless, a comparison of medical costs per day showed no significant differences between the groups ($p = 0.163$). The number of deaths during hospitalization was one in Young and Super-old, two in Pre-old, and four in Old patients.

Discussion

This retrospective study in Japan, involving 393 hospitalized patients with pyelonephritis due to *E. coli* compared the activities of daily living and medical costs between different age groups. Pyelonephritis in patients aged 75 and older was associated with a decline in ADL, longer hospital stays, and higher medical costs than in younger patients. Pre-old patients did not have lower ADL; however, they tended to have longer hospital stays and higher medical costs.

In our study, the Young and Pre-old groups did not experience a decline in BI at admission. By contrast, the Old and Super-old groups demonstrated lower BI scores upon admission. However, they showed improvement in scores from admission to discharge. This finding suggests that the acute pyelonephritis causes a temporary reduction in BI, which can be improved by adequate medical intervention. The impact of the acute pyelonephritis burden differed between the Pre-old group and the Old and Super-old groups. Thus, it may be more appropriate to distinguish individuals between the ages of 65–75 and those over 75 years when evaluating the physical impact of acute pyelonephritis, instead of grouping all 65 years and older together.

Our study observed that medical costs were higher in the older age groups; however, the cost per day of hospitalization remained the same among all groups. In other words, the aged 65 and older patients were hospitalized for longer periods, resulting in higher medical costs.

We considered three reasons for longer hospital stays in patients aged 65 and older with pyelonephritis. First, Pre-old, and Old patients had a higher rate of *E. coli* bacteremia. Second, it may take longer for Old and Super-old patients to adjust to hospital discharge. In our study, most Young patients and Pre-old were discharged; however, the rate of discharge to other hospitals or nursing homes increased with age. Toh *et al.* (*12*) reported that discharge to intermediate- and long-term care services was a significant factor for an increased length of hospital stay. Third, patients aged 65 and older are less likely to convert to oral antibiotics from intravenous infusions. Przybylski *et al.* (*13*) reported that the average length of hospital stays for patients who converted to oral antibiotics therapy was 1.53 days shorter than that of patients who were not converted. Therefore, Pre-old, Old, and Super-old patients aged ≥ 65 may have longer hospital stays and higher hospitalization costs than in Young patients.

In our study, patients aged 65 and older have longer intravenous antimicrobial infusion periods. In general, once a patient's condition stabilizes and oral medication becomes available, intravenous antibiotics are switched to oral agents to which the causative organism is susceptible. Clinicians should set longer intravenous treatment periods for older patients. Rieger KL *et al.* (*14*) reported that, in the treatment of bacteremic UTIs, the intravenous antibiotics-only group included more severely ill patients than the intravenous/oral group. In our study, since the patients aged 65 and older included more severely ill patients with a higher CCI than in younger patients, clinicians likely tended to complete treatment only with intravenous antibiotics.

In our study, the length of hospital stay was comparable among patients aged 65 and older. The total duration of antimicrobial therapy for pyelonephritis generally ranges from 7 to 14 days, depending on the rapidity of the clinical response and the antimicrobial chosen to complete the course (*15*). In our study, the mean length of hospitalization was 16 days, even in the Super-old group. This may be due to the implementation of rehabilitation, fewer complications during hospitalization, and a low rate of inappropriate empirical therapy. We investigated the complications during hospitalization, such as PLABSI, CLABSI, CAUTI, and CDI, and observed that the incidence of these diseases was low in each group. The rate of inappropriate empirical intravenous therapy was low in all groups. This may be because ESBL-producing *E. coli* was less prevalent in the study groups than in previous reports (*16,17*).

Our study has several limitations. First, it was conducted at the NCGM, a single tertiary hospital in Japan. Hospital characteristics and the unique Japanese medical system may have strongly influenced these results. However, it is highly likely that other countries will enter a super-aging society, such as Japan, and we believe that this study will be useful for these countries as well. Second, baseline BI scores before hospitalization were not determined. One of the exclusion criteria was certification for Japanese long-term care insurance with need levels over 3, equivalent to a BI score < 60 (*6*). Therefore, we included those who were independent and had a BI score of 60 or higher. However, the exact baseline BI score was unknown. Because the BI score at discharge does not necessarily correspond to the BI score before hospitalization, the difference in BI scores at admission and discharge may not be caused by the disease burden from pyelonephritis. Third, as mentioned above, our study included patients who were independent in ADL. Because bedridden older patients with declining ADL were excluded, there may be a discrepancy with the actual clinical practice. Fourth, the effects of diseases other than pyelonephritis that occurred at the time of admission or during hospitalization cannot be excluded. Fifth, we did not use indicators other than BI scores to assess ADL, such as the Comprehensive Geriatric Assessment and Lawton-Brody Instrumental Activities of Daily Living Scale (*18*), because we were unable to collect any corresponding information from the medical records.

In conclusion, in our study, even in the Super-old group, the mortality rate of hospitalized patients with pyelonephritis was low. Pyelonephritis due to *E. coli* in patients aged 75 and older is associated with a decline in ADL, longer hospital stays, and higher medical costs than that in young patients. Pre-old patients did not have lower ADL; however, they tended to have longer hospital stays and higher medical costs. Therefore, when evaluating the physical impact of acute pyelonephritis, it would be more appropriate to distinguish between the ages of 65–74 and those over 75 years, rather than lumping those aged 65 and older together as older adults.

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