



## RESEARCH

# Clinical and economic evaluation of the impact of methicillin resistance on prosthetic joint infections

Metisilin direncinin protez eklem enfeksiyonlarına olan etkisinin klinik ve ekonomik sonuçlarının değerlendirmesi

Fatma Yekta Ürkmez<sup>1</sup>, Süleyman Kaan Öner<sup>2</sup>, Sevil Alkan<sup>3</sup>, Süleyman Kozlu<sup>2</sup>

<sup>1</sup>Kirikkale Yüksek İhtisas Hospital, Kirikkale, Türkiye

<sup>2</sup>Kutahya Health Sciences University, Kütahya, Türkiye

<sup>3</sup>Canakkale Onsekiz Mart University, Canakkale, Türkiye

### Abstract

**Purpose:** Prosthetic joint infection (PJI) is unfortunately a costly process. In this study, we aimed to examine the effect of methicillin resistance on the cost of PJI compared to susceptible patients.

**Materials and Methods:** Patients who underwent primary hip or knee arthroplasty in our center between January 2012 and December 2021 and were diagnosed with staphylococcal PJI were included in this retrospective design study. Expenses incurred during hospitalization were divided into categories. Each expense was converted to dollars (\$) at the annual average exchange rate.

**Results:** A total of 55 patients were included in the study. There were 31 and 24 patients in the methicillin-resistant and susceptible groups, respectively. The methicillin-resistant group was significantly older than the susceptible group, other characteristics were similar. The cost in the methicillin-resistant group was \$2055.7 (\$676.0-\$12620.0) and in the susceptible group was \$1643.9 (\$707.8-\$10834.8). There was a statistically significant difference between the two groups in terms of surgical costs, antibiotic costs, blood center costs and radiology costs.

**Conclusion:** According to our study, the treatment cost of methicillin-resistant staphylococcus PJI was 1.3 times higher than that of methicillin-susceptible.

**Keywords:** Primary arthroplasty, antimicrobial resistance, health expenditure, economic burden, cost.

### Öz

**Amaç:** Protez eklem enfeksiyonu (PEE) maalesef maliyetli bir süreçtir. Bu çalışmada metisilin direncinin PEE maliyetine olan etkisini duyarlı hastalarla karşılaştırmayı amaçladık.

**Gereç ve Yöntem:** Ocak 2012 ile Aralık 2021 arasında merkezimizde primer kalça veya diz artroplastisi geçiren ve stafilocok PJI tanısı alan hastalar çalışmaya dahil edildi. Hastanede yatış sırasında oluşan masraflar kategorilere ayrıldı. Her masraf yıllık ortalama döviz kuru üzerinden dolara (\$) çevrildi.

**Bulgular:** Çalışmaya toplam 55 hasta dahil edildi. Metisiline dirençli ve duyarlı gruplarda sırasıyla 31 ve 24 hasta vardı. Sadece metisiline dirençli grubun yaşı duyarlı gruptan daha yüksekti, diğer özellikler benzerdi. Metisiline dirençli grupta maliyet 2055,7 \$ (676,0-12620,0 \$) ve duyarlı grupta 1643,9 \$ (707,8-10834,8 \$) idi. Bunun başlıca nedenleri cerrahi maliyetler, antibiyotik maliyetleri, kan merkezi maliyetleri ve radyoloji maliyetleriydi.

**Sonuç:** Çalışmamıza göre metisiline dirençli stafilocok PJI'nin tedavi maliyeti metisiline duyarlı olandan 1,3 kat daha yüksekti.

**Anahtar kelimeler:** Primer artroplastisi, antimikrobiyal direnç, sağlık harcaması, ekonomik yük, maliyet.

## INTRODUCTION

Life expectancy has been prolonged with technological developments and this has led to an

increase in arthroplasty applications<sup>1</sup>. Prosthetic joint infections (PJI) is one of the undesirable results accompanying arthroplasty applications<sup>2,3</sup>. PJI can be seen with an incidence of 1- 2.1%, and nowadays,

Address for Correspondence: Süleyman Kaan Öner, Kutahya Health Sciences University, Department of Orthopedics and Trauma Surgery, Kütahya, Türkiye Email: skaanoner@gmail.com

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with the increase in patients undergoing arthroplasty, an increase is observed in these infections<sup>2,3</sup>.

Undoubtedly, the development of PJI causes an economic loss<sup>3</sup>. The expenditures for PJI in the United States of America (USA) were \$320 million in 2001 and this value reached \$566 million in 2009<sup>4</sup>. Although we do not know exactly how much is spent for PJI in 2020 and beyond, studies indicate a high amount of \$1.62 million<sup>4</sup>. Even when evaluated only in terms of the expenditures made during the hospitalization period, approximately 3.4 times more expenditure occurs for patients who develop PJI than those who do not develop PJI<sup>3,4</sup>. In addition, it is not difficult to predict that this increase will be higher considering the ongoing outpatient treatment process, outpatient clinic visits and loss of working time after discharge<sup>3</sup>.

Antibiotic resistance is an increasing problem<sup>5</sup>. Approximately half of the microorganisms isolated in PJI are staphylococci, and methicillin resistance is detected in almost half of them<sup>6-8</sup>. Unfortunately, antimicrobial resistance may be associated with treatment failure or adverse outcomes<sup>9,10</sup>. Economic burden due to the treatment of resistant microorganisms is the invisible side of the iceberg<sup>11</sup>. Due to increasing antimicrobial resistance globally, governments may have to strengthen their budgets and policies for the development of new drugs to control infections, the establishment of resistance-monitoring laboratories, and the training of health personnel.

Despite the growing recognition of PJI-related costs, few studies have specifically analyzed the economic consequences of methicillin resistance in staphylococcal PJI<sup>12</sup>. In particular, country-specific cost evaluations, especially from middle-income countries, remain underrepresented in the literature<sup>13</sup>. Therefore, investigating the cost differential between methicillin-resistant and methicillin-susceptible staphylococcal PJI in our setting may offer valuable insight into the financial burden these infections place on healthcare systems<sup>14</sup>. The aim of this study is to assess the in-hospital costs associated with methicillin-resistant versus methicillin-susceptible staphylococcal PJI based on real-world data from our center and to contribute new evidence to the growing body of literature in this field.

## MATERIALS AND METHODS

### Study design and sample

The study was conducted retrospectively and 10-year period was determined. Patients over the age of 18 who underwent primary arthroplasty to the knee or hip joint in our center between January 2012 and December 2021 and were followed up after being hospitalized with the diagnosis of staphylococcal PJI were included. Those who underwent revision arthroplasty, developed polymicrobial PJI, and follow-up could not be completed due to death during the PJI treatment were excluded from the study. In addition, the costs after discharge from the hospital (outpatient clinic visits, antibiotics, etc.) were not evaluated because the data could not be reached reliably.

Ethics committee approval was obtained from the Kırıkkale University Ethics Committee (Decision No: 2022.06.24, dated 29.06.2022)."

A post hoc power analysis was conducted using G\*Power version 3.1 to assess the statistical adequacy of the study. Based on an assumed effect size of 0.7, a significance level ( $\alpha$ ) of 0.05, and a target statistical power of 80%, the minimum required sample size was determined to be 33 subjects per group. In the present study, a total of 55 patients met the eligibility criteria and were included in the final analysis, comprising 31 patients in the methicillin-resistant group and 24 in the methicillin-susceptible group. With this sample distribution, the calculated statistical power was 71.5%. Although slightly below the conventional threshold of 80%, this power level may be considered acceptable for exploratory clinical research, particularly given the rarity of prosthetic joint infections and the retrospective nature of the study.

The inclusion criteria for this retrospective study were as follows:

- (1) patients aged 18 years or older,
- (2) individuals who underwent primary total hip or knee arthroplasty at our institution between January 2012 and December 2021, and
- (3) those who were diagnosed with prosthetic joint infection (PJI) caused by *Staphylococcus* species, in accordance with the 2012 Infectious Diseases Society of America (IDSA) diagnostic criteria.

Exclusion criteria included:

- (1) patients who underwent revision arthroplasty during the index procedure,
- (2) polymicrobial PJI confirmed by culture results,
- (3) incomplete clinical or cost data, including patients who died or were discharged before completing treatment, and
- (4) PJI caused by non-staphylococcal organisms such as Gram-negative bacteria or fungi.

A total of 68 patients were initially screened based on surgical and microbiological records. Following the application of exclusion criteria: 7 patients were excluded due to polymicrobial infections, 4 patients due to incomplete follow-up data (e.g., death or early discharge), and 2 patients due to infection with non-staphylococcal microorganisms. After exclusions, 55 patients with confirmed Staphylococcus-related PJI met all criteria and were included in the final analysis.

### Diagnostic criteria and classification

The criteria of the Infectious Diseases Society of America (IDSA) 2012 guidelines were used for the diagnosis of PJI.<sup>15</sup> Similarly, PEE classification was made according to the IDSA guideline and categorized as early, delayed, and late<sup>15</sup>. Patients diagnosed with staphylococcal PJI were divided into two groups as methicillin resistant and methicillin susceptible according to the susceptibility of the isolated strains.

### Data collection

The data of the patients were obtained from the hospital archive records and the hospital automation system. While determining the comorbid conditions of the patients, ICD-10 (International Statistical Classification of Diseases and Related Health Problems) codes in the hospital automation system were used.

### Cost analysis

The expenses incurred during the hospitalization period for the patients were obtained from the billing unit. Expenditures on each invoice were individually evaluated and categorized. These categories were hospitalization expenditures, operation expenditures, antibiotic expenditures, blood center expenditures, radiology expenditures, laboratory expenditures, microbiology expenditures, consultation expenditures and total expenditures. Each of the

expenditures was converted into dollars (\$) according to the average exchange rate of the Central Bank of the Republic of \* for that year.

This study was conducted at the Kırıkkale High Specialization Hospital, Department of Infectious Diseases and Clinical Microbiology, a tertiary referral center with extensive experience in the management of musculoskeletal infections. All diagnostic evaluations, microbiological sampling, and treatment decisions for prosthetic joint infections (PJI) were performed by board-certified infectious disease specialists in collaboration with orthopedic surgeons.

The clinical and financial data were obtained from the hospital's electronic medical record system and institutional billing database, both of which are maintained under standardized national protocols and regularly audited for accuracy. The diagnosis, antimicrobial treatment, and hospitalization records were documented in real time by attending physicians and reviewed by senior consultants to ensure data reliability.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Since most variables were not normally distributed, non-parametric tests were employed. Comparison of continuous variables (e.g., age, hospitalization duration, surgical costs, antibiotic expenditures) between the methicillin-resistant and methicillin-susceptible groups was performed using the Mann–Whitney U test. Categorical variables (e.g., sex, comorbidities, surgical treatment strategy, infection classification, causative microorganism) were analyzed using the Chi-square test or Fisher's exact test where appropriate, depending on expected cell frequencies. Descriptive statistics were reported as median (min–max) for continuous variables and frequency (percentage) for categorical variables. A p-value < 0.05 was considered statistically significant for all comparisons. This approach ensured an appropriate statistical evaluation of both demographic and cost-related variables in relation to methicillin resistance.

## RESULTS

A total of 55 patients who underwent total knee or

hip arthroplasty between January 2012 and December 2021 and subsequently developed staphylococcal PJI were included in the study. 31 (56.5%) were in the methicillin resistant group, 24 (43.6%) were in the methicillin susceptible group. The median age of cases infected with methicillin resistant staphylococci was 70, while it was 63 in susceptible cases ( $p=0.043$ ). Gender, length of stay in

hospital and intensive care unit, comorbidities were similar in both groups. In addition, infection classification, surgical treatment plan, and microorganisms isolated in culture were similar in both groups. Demographic characteristics, operation characteristics and causative microorganism characteristics of methicillin resistant and susceptible staphylococcal PJI groups are presented in Table 1.

**Table 1. Demographic characteristics, operation characteristics and causative microorganism characteristics of methicillin resistant and susceptible staphylococcal PJI groups.**

|                                  | Methicillin resistant (n=31) | Methicillin sensitive (n=24) | p     |
|----------------------------------|------------------------------|------------------------------|-------|
| Median (min- max)                |                              |                              |       |
| Age (years)                      | 70 (48- 87)                  | 63 (43- 82)                  | 0.043 |
| Days of hospitalization          | 28 (10- 245)                 | 27 (8- 75)                   | 0.959 |
| Days of hospitalization in ICU   | 0 (0- 27)                    | 0 (0-30)                     | 0.338 |
| n (%)                            |                              |                              |       |
| Sex (male)                       | 9 (29.0%)                    | 9 (37.5%)                    | 0.507 |
| Comorbidity                      |                              |                              |       |
| Diabetes mellitus                | 11 (35.5%)                   | 8 (33.3%)                    | 0.868 |
| Cardiovascular disease           | 21 (67.7%)                   | 13 (54.2%)                   | 0.304 |
| Renal disease                    | 2 (6.5%)                     | 5 (20.8%)                    | 0.112 |
| Respiratory system disease       | 8 (25.8%)                    | 2 (8.3%)                     | 0.096 |
| Neurologic disease               | 3 (9.7%)                     | 1 (4.2%)                     | 0.435 |
| Malignity                        | 0 (0%)                       | 1 (4.2%)                     | 0.251 |
| Rheumatologic disease            | 2 (6.5%)                     | 0 (0%)                       | 0.205 |
| Site of surgery                  |                              |                              |       |
| Hip                              | 14 (45.2%)                   | 7 (29.2%)                    | 0.226 |
| Knee                             | 17 (54.8%)                   | 17 (70.8%)                   |       |
| Indication of the surgery        |                              |                              |       |
| Osteoarthritis                   | 23 (74.2%)                   | 22 (91.7%)                   | 0.096 |
| Fracture                         | 8 (25.8%)                    | 2 (8.3%)                     |       |
| PJI onset                        |                              |                              |       |
| Early                            | 19 (61.3%)                   | 18 (75%)                     | 0.249 |
| Delayed                          | 9 (29.0%)                    | 6 (25%)                      |       |
| Late                             | 3 (9.7%)                     | 0 (0%)                       |       |
| Surgical treatment plan          |                              |                              |       |
| DAIR                             | 8 (25.8%)                    | 8 (33.3%)                    | 0.748 |
| One-stage revision               | 7 (22.6%)                    | 6 (25%)                      |       |
| Two-stage revision               | 16 (51.6%)                   | 10 (41.7%)                   |       |
| Culture results                  |                              |                              |       |
| Staphylococcus aureus            | 11 (35.5%)                   | 10 (41.7%)                   | 0.219 |
| Coagulase negative staphylococci | 20 (64.5%)                   | 14 (58.3%)                   |       |

Mann Whitney U and chi square tests were employed.; Values are presented as median (min- max) or number (%); ICU: Intensive Care Unit.; DAIR: Debridement, Antibiotics, and Implant Retention.

Considering the expenditures of methicillin resistant and susceptible staphylococcal PJI groups; while the median value spent per patient was \$2055.7 (\$676.0- \$12620.0) in the resistant group, it was \$1643.9 (\$707.8- \$10834.8) in the susceptible group

( $p=0.039$ ). Hospitalization expenditures, intensive care expenditures, laboratory expenditures, microbiology expenditures and consultation expenditures were similar between the two groups. Surgical expenses were \$809.9 (\$416.1- \$1124.7) and

\$597.4 (\$369.2- \$1106.8) in the resistant and susceptible groups, respectively ( $p=0.029$ ). Considering the antibiotic expenditures, it was significantly higher in the methicillin resistant group

( $p=0.043$ ). A comparison of the costs of patients who developed PJI with methicillin-resistant and susceptible staphylococci is presented in Table 2.

**Table 2. Comparison of costs of methicillin resistant and susceptible staphylococcal PJI**

| Per patient expenses (\$)   | Methicillin resistant (n=31) | Methicillin sensitive (n=24) | p     |
|-----------------------------|------------------------------|------------------------------|-------|
| Hospitalization costs       | 383.5 (82.8- 4474.8)         | 365.3 (142.4- 1102.9)        | 0.690 |
| ICU hospitalization costs   | 0 (0- 6357.6)                | 0 (0- 8823.5)                | 0.351 |
| Total hospitalization costs | 529.4 (82.8- 6663.0)         | 365.3 (142.4- 9926.3)        | 0.203 |
| Surgical costs              | 809.9 (416.1- 1124.7)        | 597.4 (369.2- 1106.8)        | 0.029 |
| Antibiotic costs            | 253.1 (43.1- 4619.1)         | 166.9 (49.4- 542.1)          | 0.043 |
| Blood center costs          | 99.5 (0- 587.8)              | 0 (0- 796.4)                 | 0.044 |
| Radiology costs             | 35.7 (11.3- 112.9)           | 25.4 (5.1- 92.1)             | 0.034 |
| Laboratory costs            | 210.4 (38.1- 951.9)          | 170.4 (53.2- 1073.6)         | 0.175 |
| Microbiology costs          | 23.8 (7.7- 94.1)             | 27.6 (5.3- 72.6)             | 0.747 |
| Consultation costs          | 24.2 (3.9- 207.1)            | 19.1 (4.9- 161.0)            | 0.154 |
| Total cost per patient      | 2055.7 (676.0- 12620.0)      | 1643.9 (707.8- 10834.8)      | 0.039 |

Mann Whitney U test was employed.; Values are presented as median (min- max).; ICU: Intensive Care Unit.

## DISCUSSION

In this study, we found that the cost per patient was \$2055.7 in the presence of methicillin resistance... This aligns with findings by Akindolire et al., who reported a substantial economic impact of PJI in total hip arthroplasty settings<sup>15-18</sup>. Additionally, recent reviews such as that of Aftab et al. underscore how antimicrobial resistance compounds both the direct treatment costs and long-term burden of PJI<sup>19</sup>.

The study of Parvizi et al. is the first and only study in the available literature to compare the costs of methicillin resistant and susceptible PJI<sup>11</sup>. In this study, the cost of methicillin resistant PJI was reported as \$107264, and the cost of methicillin susceptible PJI was reported as \$68053 ( $p<.0001$ )<sup>11</sup>. According to this study, the presence of methicillin resistance increases the cost 1.6 times compared to susceptible strains<sup>11</sup>. Similarly, in our study, the cost increased 1.3 times in the presence of methicillin resistance. The fact that the cost per patient in our country is less than the study of Parvizi et al. touches on a very important point in terms of health tourism.

In our study, surgical expenses were found to be significantly higher in the methicillin resistant group. However, we found that the surgical treatment strategies applied to the patients were similar between the two groups. These findings may be due to treatment failure and the need for repeated surgical treatment in the methicillin resistant group. Possible repeat procedures, increased use of implants, or

extended operating room time are among the reasons for increased surgical costs PJI in the methicillin-resistant group.

The price of antimicrobial agents used in the treatment of resistant microorganisms may be higher than the agents that can be used in susceptible microorganisms. In addition, in the treatment of resistant microorganisms, combination therapies are also required in some cases. In our study, although the duration of hospitalization was similar in both groups, the higher antibiotic expenditures in the methicillin resistant group can be explained by the higher prices of these agents. Antibiotic costs vary depending on resistance status, and agents such as vancomycin or linezolid, which are frequently used to treat methicillin-resistant *Staphylococcus aureus* (MRSA), are significantly more costly than standard antibiotics<sup>15, 16</sup>.

In various studies, the mean age of patients with methicillin resistant staphylococcal PJI was reported to be between 63-73 years<sup>11, 15-17</sup>. When methicillin resistant and susceptible groups were compared, the ages were reported to be similar<sup>11</sup>. In our study, the median age of the methicillin resistant group was 70 years, and it was significantly higher than the methicillin susceptible group. It is thought that this finding can be explained by the higher number of hospital admissions or antibiotic use in older patients for various reasons, and the corresponding increase in the development of antimicrobial resistance.

In studies, it was determined that 46- 51% of patients with methicillin resistant and susceptible staphylococcal PJI were male, and no difference was reported between the group <sup>11,15-17</sup>. Similarly, in our study, there was no difference between the two groups, but 29- 38% of our patients were male, and this rate was found to be lower than in other studies.

When the patients who developed PJI with methicillin resistant and susceptible strains were evaluated in terms of hospitalization period; It is observed that the duration of hospitalization is longer in methicillin resistant PJI patients than in the susceptible group (38.13 vs 21.38 days, respectively,  $p=0.0001$ )<sup>11</sup>. However, in our study, the length of hospital stay was similar between the two groups and was approximately 28 days. It is thought that these periods are similar between the groups, as the patients are discharged as soon as possible to prevent nosocomial infections, and the continuation of outpatient parenteral treatment at home or in primary care centers, and the patients are followed up with outpatient clinic visits.

The rates of *S. aureus* and coagulase-negative staphylococci (CNS) identified as PJI agents differ in studies in the literature. In a study published in 2014 in which PJI factors in the USA and Europe were evaluated; In USA, 31% of all PJI agents were *S. aureus* and 20.2% were CNS; In Europe, *S. aureus* is seen in 13% and CNS in 39.3%.<sup>7</sup> In a study by Barberan et al. in Spain, 21 of the isolated agents in elderly patients with PJI were *S. aureus*, while 39 were CNS <sup>6</sup>. Similarly, in our study, *S. aureus* was found in 21 patients and CNS in 34 patients.

When staphylococci that cause PJI are evaluated in terms of methicillin resistance; in studies in the literature, methicillin resistance was found in 33.3% of *S. aureus* isolates <sup>6</sup>. In our study, methicillin resistance was found in 52.4% of *S. aureus* isolates and 58.8% of CNS. Considering that this study was published in 2006, increasing antibiotic resistance over the years is strikingly detected.

Despite its limitations, this study provides valuable insight into the real-world cost implications of antimicrobial resistance in PJI management. Future multicenter studies incorporating outpatient costs, long-term follow-up, and indirect expenses such as productivity loss are warranted to fully understand the socioeconomic burden of resistant infections. Additionally, cost-effectiveness analyses comparing different therapeutic approaches including prolonged

antibiotic therapy, outpatient parenteral antimicrobial therapy (OPAT), and surgical strategies may guide resource allocation and clinical decision-making. Establishing national registries for PJI with resistance profiling and cost data could further support health policy planning and infection control strategies in similar healthcare settings.

Our study is very important in that it is the second study in the literature comparing the cost of methicillin resistant and susceptible staphylococcal PJI, and the first study in our country, and this fact constitutes the strength of our study. However, only the evaluation of the costs incurred during the hospitalization process and the exclusion of the costs incurred during the outpatient clinic visits are the limitations of our study. Another limitation of our study is that it was single-centered and designed retrospectively.

Antibiotic resistance is unfortunately a growing problem. While PJI is a problem in itself, resistant microorganisms make it more difficult to follow and treat. As a result of our study, we found that the cost of treatment of methicillin resistant staphylococcal PJI increased 1.3 times compared to methicillin susceptible ones. The main reasons for this were surgical expenditures, antibiotic expenditures, blood center expenditures and radiology expenditures. Considering the ongoing outpatient parenteral treatment and oral antibiotic treatments after discharge, and outpatient visits, this difference seems likely to increase. Our study provides guidance on the effect of methicillin resistance on the cost in patients with PJI and reveals that the economic burden due to PJI can reach greater dimensions when combined with antimicrobial resistance. However, our study only evaluated the expenses incurred during the hospitalization process, and further studies are needed that include outpatient treatments and even take into account socioeconomic aspects such as loss of workforce and productivity.

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