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Original Article

ANALYSIS OF DRUG UTILIZATION AND DIRECT MEDICAL COSTS AMONG PATIENTS WITH KNEE OSTEOARTHRITIS WITH AND WITHOUT RECORDED HYALURONIC ACID USE AT THONG NHAT HOSPITAL, HO CHI MINH CITY

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ABSTRACT: Intra-articular hyaluronic acid (HA) is used to treat knee osteoarthritis; however, data on medication utilization patterns and healthcare costs in Vietnam remain limited. This retrospective observational study analyzed electronic medical records, medication utilization data, and billing records of patients with knee osteoarthritis with and without recorded HA use at Thong Nhat Hospital during 2024–2025. Among 25,575 patients with an ICD-10 M17.x diagnosis, 894 (3.5%) were classified into the HA group and 24,681 into the non-HA group. Patients in the HA group were older on average (65.7 vs. 61.0 years) and more likely to be female (77.9% vs. 63.0%). Compared with the non-HA group, the HA group had lower proportions of visits involving NSAIDs (45.0% vs. 57.5%) and analgesics (24.5% vs. 31.7%), but a higher proportion involving symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) (29.5% vs. 26.3%). In the primary analysis restricted to patients with at least 30 days of available observation (n=25,365), the median annualized direct medical cost was VND 13.23 million per person-year [8.07–24.11] in the HA group and VND 1.86 million per person-year [0.88–3.79] in the non-HA group ($p<0.001$). After adjustment, annualized costs were higher in the HA group than in the non-HA group (adjusted cost ratio: 4.833; 95% CI: 4.019–5.874; $p<0.001$). These findings reflect differences in medication utilization patterns and costs between the two groups in routine hospital practice.

Keywords: knee osteoarthritis; hyaluronic acid; medication utilization; direct medical costs; real-world data.

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1. INTRODUCTION

Knee osteoarthritis (KOA) is one of the most common musculoskeletal disorders worldwide [1] and often leads to chronic pain, joint stiffness, limited mobility, and reduced quality of life [2]. According to Global Burden of Disease estimates for 2020, approximately 595 million people (7.6% of the world population) were living with osteoarthritis, and this number will continue to rise [1].

Beyond its clinical impact, KOA imposes an economic burden on patients because of the need for long-term treatment [3]. Treatment of KOA aims to relieve pain, improve function, and maintain mobility. In addition to non-pharmacological measures such as weight loss and physical therapy, several drug classes are used in practice, including non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, capsaicin, symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), and intra-articular injections [4–6]. Intra-articular hyaluronic acid (HA) is used to supplement the elastic and lubricating properties of synovial fluid, thereby helping to relieve pain and improve joint function [7]. However, HA use also involves direct medical costs, such as the costs of the drug, the injection procedure, consultations, and related services [3,8]. In addition, patients often also use several other drug classes in combination, which increases total treatment costs [9].

Although several studies have examined the effectiveness and costs of KOA treatment [3,8–10], real-world data from Vietnamese hospitals on medication use patterns and direct medical costs in patients with and without recorded HA use remain limited. We therefore analyzed the use of KOA medications and direct medical costs in patients with and without recorded HA use at Thong Nhat Hospital to provide information on treatment practice and resource use at the hospital and to inform further health economic studies.

2. SUBJECTS AND METHODS

2.1. Study subjects

Patients with KOA who had consultation, medication, and billing data at Thong Nhat Hospital during the study period.

Inclusion criteria: Patients were included if they had at least one visit with ICD-10 M17.x recorded as the primary or secondary diagnosis and, after the visit selection criteria were applied, at least one valid visit remained for analysis (this could be the index visit itself).

Exclusion criteria: Patients were excluded if their identifier could not be determined, if information was insufficient to order their visits chronologically, or if no visit eligible for analysis remained.

Visit inclusion and exclusion criteria: Each patient's visits were ordered chronologically, and the date of the first M17.x record was defined as the index date. A visit was considered valid if it (1) had M17.x as the primary or secondary diagnosis, or (2) occurred after the index date and included at least one medication or therapy related to KOA treatment, based on a list compiled from current KOA diagnosis and treatment guidelines [4,6,11]. Visits that did not meet these conditions were excluded from the analysis.

2.2. Study methods

This was a retrospective descriptive observational study using electronic medical records, medication data, and inpatient and outpatient billing data at Thong Nhat Hospital from January 2024 to December 2025.

The HA group was defined at the patient level based on the rule "HA use recorded during the study period": valid inpatient episodes with recorded HA were identified first, and all valid inpatient and outpatient visits with the same patient ID were then assigned to the HA group; the remaining patients formed the non-HA group. Data were linked by patient ID and treatment date. Demographic variables, treatment setting, length of hospital stay, and costs were analyzed at the patient level. Variables related to comorbidity diagnoses and medication use in the descriptive analysis were analyzed at the visit level. To standardize costs by observation time, available observation time was calculated from the index date to the end date of the database (31/12/2025).

Costs were aggregated at the patient level from charges incurred at valid visits, including consultations, beds, laboratory tests, diagnostic imaging, medications, medical supplies, procedures, surgery,

blood, and other items. Joint-related medication, imaging, and procedure costs were identified using a list of service codes. All costs were converted to 2026 values using the consumer price index (CPI): cost in 2026 = cost in year t × CPI 2026/CPI year t. The primary cost outcome was the annualized direct medical cost per person-year, calculated as: total cumulative cost × 365.25 / number of days of available observation. Because annualization over very short observation periods may be unstable [12], the primary model was run in patients with at least 30 days of available observation.

Regression analysis used a generalized linear model with a Gamma distribution and log link, which suits cost data that are usually positive and right-skewed [13,14]. The main dependent variable was the annualized direct medical cost per person-year. Independent variables were HA group, age, sex, health insurance (HI) coverage level, M17.x subgroup, and number of comorbidities. HI coverage of 80% and M17.0 were selected as reference categories. The regression model was run in patients with at least 30 days of available observation.

2.3. Data processing and analysis

Data were analyzed using R 4.5.3. Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± standard deviation (SD) and/or median [Q1; Q3]. Mean age was compared using the t-test; other continuous variables were compared using the Mann–Whitney U test, and categorical variables using the chi-square test. Statistical significance was set at $p<0.05$. The main dependent variable was the annualized direct medical cost per person-year. Independent variables were HA group, age, sex, HI coverage level, M17.x subgroup, and number of comorbidities. HI coverage of 80% and M17.0 were selected as reference categories. The regression model was run in patients with at least 30 days of available observation.

2.4. Research ethics

This retrospective study did not intervene in diagnosis or treatment and was approved by the Biomedical Research Ethics Committee of Thong Nhat Hospital (Certificate No. 187/2025/CN-HĐĐĐ-BVTN dated 27/10/2025).

3. RESULTS

3.1. Characteristics of the study sample

We identified 25,575 patients with KOA, of whom 894 (3.5%) were in the HA group and 24,681 (96.5%) were in the non-HA group. The HA group had a higher mean age (65.7 ± 11.5 vs. 61.0 ± 14.6 years) and

Table 1. Characteristics of the study sample by hyaluronic acid use group

Characteristic	Total (n=25,575)	HA group (n=894)	Non-HA group (n=24,681)	p-value
Age, mean ± SD	61.1 ± 14.5	65.7 ± 11.5	61.0 ± 14.6	<0.001
Age, median [Q1; Q3]	62.0 [52.0; 71.0]	66.0 [59.2; 74.0]	62.0 [52.0; 71.0]	<0.001
Age group	<0.001			
<50	5,271 (20.6)	72 (8.1)	5,199 (21.1)	
50-59	5,698 (22.3)	152 (17.0)	5,546 (22.5)	
60-69	7,355 (28.8)	340 (38.0)	7,015 (28.4)	
70-79	4,546 (17.8)	237 (26.5)	4,309 (17.5)	
≥80	2,705 (10.6)	93 (10.4)	2,612 (10.6)	
Sex (female)	16,242 (63.5)	696 (77.9)	15,546 (63.0)	<0.001
Treatment setting during observation	<0.001			
Outpatient only	23,285 (91.0)	0 (0.0)	23,285 (94.3)	
Inpatient only	1,028 (4.0)	213 (23.8)	815 (3.3)	

Both outpatient and inpatient	1,262 (4.9)	681 (76.2)	581 (2.4)	
HI coverage level	<0.001			
80%	14,201 (55.5)	291 (32.6)	13,910 (56.4)	
95%	4,585 (17.9)	202 (22.6)	4,383 (17.8)	
100%	6,068 (23.7)	218 (24.4)	5,850 (23.7)	
No HI recorded	721 (2.8)	183 (20.5)	538 (2.2)	
≥1 visit with M17.x as primary diagnosis	11,416 (44.6)	794 (88.8)	10,622 (43.0)	<0.001
Total inpatient days/patient	0 [0; 0]	8 [3; 18]	0 [0; 0]	<0.001
Total valid visits/patient	3.0 [1.0; 6.0]	8.0 [4.0; 16.0]	2.0 [1.0; 6.0]	<0.001
Time from index date to last valid visit (days)	138 [0; 403]	473.5 [221.8; 634.0]	126 [0; 391]	<0.001
Available observation time to 31/12/2025 (days)	464.0 [267.0; 632.0]	637.5 [470.0; 707.0]	462.0 [260.0; 625.0]	<0.001

a higher proportion of women (77.9% vs. 63.0%). All patients in the HA group had at least one inpatient episode, whereas 94.3% of patients in the non-HA group had outpatient visits only. HI coverage levels also differed between the two groups (Table 1).

Data are presented as frequency (%), mean ± SD, or median [Q1; Q3]. The unit of analysis is the patient. Mean age was compared using the t-test, skewed continuous variables using the Mann–Whitney U test, and categorical variables using the chi-square test. Time from the index date to the last valid visit and available observation time up to 31/12/2025 are presented separately.

3.2. Characteristics of knee osteoarthritis

Of 120,119 valid visits, 9,943 were in the HA group and 110,176 in the non-HA group. M17.x was recorded as the primary diagnosis in 46.5% of visits in the HA group and 20.8% of visits in the non-HA group.

Table 2. Characteristics of knee osteoarthritis by HA use group

Characteristic	Total (n = 120,119 visits)	HA group (n = 9,943 visits)	Non-HA group (n = 110,176 visits)
M17.x as primary diagnosis	27,551 (22.9)	4,626 (46.5)	22,925 (20.8)
M17.x subgroup			
M17.0 – Bilateral primary KOA	71,656 (59.7)	7,173 (72.1)	64,483 (58.5)
M17.1 – Other primary KOA	1,562 (1.3)	80 (0.8)	1,482 (1.3)
M17.2 – Bilateral post-traumatic KOA	46 (0.0)	7 (0.1)	39 (0.0)
M17.3 – Other post-traumatic KOA	427 (0.4)	45 (0.5)	382 (0.3)
M17.4 – Other bilateral secondary KOA	163 (0.1)	16 (0.2)	147 (0.1)
M17.5 – Other secondary KOA	215 (0.2)	18 (0.2)	197 (0.2)
M17.9 – KOA, unspecified	3,520 (2.9)	155 (1.6)	3,365 (3.1)
Multiple M17.x codes in one visit	283 (0.2)	30 (0.3)	253 (0.2)

M17.x, subgroup not specified	764 (0.6)	352 (3.5)	412 (0.4)
Number of comorbidities			
Mean ± SD	4.6 ± 2.8	3.6 ± 3.1	4.7 ± 2.7
Median [Q1; Q3]	4.0 [2.0; 6.0]	3.0 [1.0; 6.0]	4.0 [3.0; 6.0]
Five most commonly recorded comorbidities			
Hypertension (I10)	50,067 (41.7)	3,824 (38.5)	46,243 (42.0)
Mixed hyperlipidemia (E78.2)	40,669 (33.9)	2,144 (21.6)	38,525 (35.0)
Gastro-esophageal reflux disease (K21.9)	35,551 (29.6)	2,680 (27.0)	32,871 (29.8)
Chronic venous insufficiency (I87.2)	23,072 (19.2)	2,020 (20.3)	21,052 (19.1)
Type 2 diabetes without complications (E11.9)	15,663 (13.0)	888 (8.9)	14,775 (13.4)

M17.0 was the most common subgroup, accounting for 72.1% and 58.5% of visits in the two groups, respectively. The mean number of comorbidities per visit was lower in the HA group than in the non-HA group (3.6 ± 3.1 vs. 4.7 ± 2.7) (Table 2).

Data are presented as frequency (%), mean ± SD, or median [Q1; Q3]. The unit of analysis is the visit. Each visit was assigned to one M17.x subgroup; visits with more than one M17.x code are presented separately.

3.3. Medication use in patients with knee osteoarthritis

NSAIDs were the most frequently recorded drug class, accounting for 56.5% of all visits. The HA group had lower proportions of visits with recorded NSAIDs and analgesics than the non-HA group (45.0% vs. 57.5% and 24.5% vs. 31.7%, respectively), whereas the proportion with SYSADOAs was higher (29.5% vs. 26.3%). HA was recorded at 2,643 visits, corresponding to 26.6% of visits in the HA group (Table 3).

Table 3. Use of knee osteoarthritis medications at the visit level

Drug class	Total (n=120,119), n (%)	HA group (n=9,943), n (%)	Non-HA group (n=110,176), n (%)
Hyaluronic acid	2,643 (2.2)	2,643 (26.6)	0 (0.0)
NSAID	67,872 (56.5)	4,479 (45.0)	63,393 (57.5)
Analgesics (paracetamol/ opioids)	37,370 (31.1)	2,441 (24.5)	34,929 (31.7)
Capsaicin	2,854 (2.4)	234 (2.4)	2,620 (2.4)
SYSADOA	31,874 (26.5)	2,932 (29.5)	28,942 (26.3)
Bisphosphonates	10,523 (8.8)	604 (6.1)	9,919 (9.0)
PRP/cell therapy	104 (0.1)	28 (0.3)	76 (0.1)

3.4. Direct medical costs

The median total cumulative direct medical cost was VND 20.61 [11.21; 37.83] million/patient in the HA group, compared with VND 1.66 [0.73; 4.00] million/patient in the non-HA group ($p<0.001$). In the analysis cohort with at least 30 days of available observation (n=25,365;

Table 4. Direct medical costs of KOA treatment by HA use group (Unit: VND).

Cost item	Total (n=25,575)	HA group (n=894)	Non-HA group (n=24,681)	p-value
Total cumulative direct medical cost	1,767,172 [752,865; 4,496,511]	20,611,970 [11,208,385; 37,833,190]	1,664,527 [732,624; 3,996,010]	<0.001
Annualized direct medical cost per person-year (cohort ≥30 days; n=25,365; HA=893; non-HA=24,472)	1,950,021 [906,672; 4,115,065]	13,229,243 [8,074,160; 24,114,015]	1,864,123 [878,009; 3,785,103]	<0.001
Outpatient costs	1,474,352 [633,796; 3,442,916]	2,581,310 [263,514; 7,285,354]	1,457,988 [639,903; 3,359,082]	<0.001
Inpatient costs	0 [0; 0]	14,679,900 [7,817,285; 30,818,307]	0 [0; 0]	<0.001
Mean cost per visit	614,540 [405,114; 928,123]	2,120,590 [1,341,343; 4,972,084]	599,356 [399,555; 882,692]	<0.001
Costs by component				
Medications	854,424 [349,634; 2,537,226]	9,635,322 [6,178,254; 16,652,921]	800,272 [339,980; 2,206,220]	<0.001
Laboratory tests	0 [0; 431,300]	867,750 [345,775; 1,698,225]	0 [0; 403,200]	<0.001
Diagnostic imaging	221,600 [0; 611,200]	846,400 [311,225; 2,020,375]	210,600 [0; 581,900]	<0.001
Joint ultrasound	0 [0; 49,300]	49,300 [0; 58,600]	0 [0; 0]	<0.001
Procedures	0 [0; 0]	626,400 [577,200; 1,203,600]	0 [0; 0]	<0.001
Intra-articular injection	0 [0; 0]	626,400 [417,600; 626,400]	0 [0; 0]	<0.001
Surgery	0 [0; 0]	0 [0; 1,411,612]	0 [0; 0]	<0.001
Bed	0 [0; 0]	1,905,900 [821,400; 5,286,050]	0 [0; 0]	<0.001
Medical supplies	0 [0; 0]	70,982 [23,965; 538,494]	0 [0; 0]	<0.001
Consultation	131,560 [64,768; 320,200]	216,550 [42,100; 651,621]	131,560 [65,780; 312,510]	<0.001
Other	0 [0; 0]	0 [0; 5,000]	0 [0; 0]	<0.001
Joint-treatment medication/therapy costs				

Total joint-treatment medication costs	305,388 [105,860; 737,077]	6,490,932 [4,231,966; 8,631,218]	287,700 [98,250; 655,554]	<0.001
Hyaluronic acid	0 [0; 0]	5,240,000 [3,180,000; 6,270,000]	0 [0; 0]	-
NSAID	137,564 [4,620; 348,498]	381,842 [107,416; 972,538]	137,000 [4,620; 333,704]	<0.001
Analgesics	2,660 [0; 13,622]	13,702 [1,950; 81,046]	2,660 [0; 13,232]	<0.001
SYSADOA	22,512 [0; 336,000]	454,900 [84,000; 970,088]	19,656 [0; 300,000]	<0.001

*Note: Data are presented as median [Q1; Q3]. Cumulative costs and cost components are in VND/patient and are described for all 25,575 patients. Annualized costs per person-year are presented only for the primary analysis cohort with ≥30 days of available observation (n=25,365; HA=893; non-HA=24,472), in VND/person-year. Infrequent cost components have a median [Q1; Q3] of 0 [0; 0] but may still occur and are included in total costs when used.

HA=893; non-HA=24,472), the median annualized direct medical cost was VND 13.23 [8.07; 24.11] million/person-year in the HA group and VND 1.86 [0.88; 3.79] million/person-year in the non-HA group (p<0.001). In the HA group, the median cost of joint-treatment medications/therapies was VND 6.49 million/patient, of which HA cost VND 5.24 million/patient (Table 4).

3.5. Factors associated with costs

In the Gamma log-link model in

Table 5. Factors associated with annualized direct medical cost per person-year in patients with ≥30 days of available observation (n=25,365)

Variable	Adjusted cost ratio	95% CI	p-value
HA group (vs. non-HA)	4.833	4.019–5.874	<0.001
Age (per 1-year increase)	1.013	1.009–1.016	<0.001
Male (vs. female)	0.992	0.922–1.069	0.837
HI 95% (vs. 80%)	1.151	1.039–1.277	0.008
HI 100% (vs. 80%)	1.244	1.117–1.387	<0.001
No HI recorded (vs. 80%)	5.745	4.672–7.158	<0.001
M17.1 (vs. M17.0)	0.841	0.686–1.044	0.104
M17.9 (vs. M17.0)	0.918	0.793–1.070	0.261
Other/multiple M17 codes (vs. M17.0)	1.637	1.300–2.098	<0.001
M17 unspecified (vs. M17.0)	7.981	5.821–11.339	<0.001
Number of comorbidities (per comorbidity)	1.076	1.063–1.090	<0.001

patients with at least 30 days of available observation (n=25,365), the HA group had an adjusted cost ratio of 4.833 relative to the non-HA group (95% CI: 4.019–5.874; p<0.001) after adjustment for age, sex, HI coverage level, M17.x subgroup, and number of comorbidities. Age and number of comorbidities were associated with higher costs, whereas sex was not significantly associated with costs (Table 5).

4. DISCUSSION

In this study of 25,575 patients with knee osteoarthritis, 894 (3.5%) had recorded HA use. The HA group had a higher mean age and a higher proportion of women than the non-HA group, consistent with the epidemiology of the disease [1]. Comorbidities were mainly cardiovascular, metabolic, and gastrointestinal, similar to a previous study at the same hospital [9].

NSAIDs were the most frequently recorded drug class, accounting for 56.5% of visits. The HA group had lower proportions of visits with recorded NSAIDs and analgesics but a higher proportion with SYSADOAs than the non-HA group. This difference may reflect differences in patient characteristics and treatment strategies rather than show that HA directly replaces NSAIDs. The HA group was older on average than the non-HA group, which fits the profile of older patients, in whom NSAID use requires consideration of gastrointestinal, renal, and cardiovascular risks; NICE recommends assessing these risk factors before using oral NSAIDs [4]. The present study did not have complete data on history of gastrointestinal bleeding, renal function, cardiovascular risk, pain severity, or reasons for treatment changes, so the specific reasons for the lower proportion of NSAID use in the HA group could not be determined.

The median total cumulative direct medical cost was VND 20.61 million/patient in the HA group and VND 1.66 million/patient in the non-HA group. In the cohort with at least 30 days of observation, the corresponding annualized costs were VND 13.23 and 1.86 million/person-year. After adjustment, the HA group had a cost ratio of 4.833. At this hospital, patients receiving HA must be admitted for the intra-articular injection procedure; the cost difference therefore reflects the whole course of treatment, including medications, hospital beds, procedures, supplies, and related services, rather than the effect of HA alone. In the HA group, HA accounted for approximately 80.7% of total joint-treatment medication/therapy costs.

A study at Nguyen Trai Hospital also found higher direct medical costs for HA than for oral medications [8], but it used a payer perspective and QALYs as the outcome, so the results cannot be compared directly. In analyses of claims data in the United States, HA accounted for only a small share of total knee osteoarthritis-related costs [15,16], whereas in the present study HA accounted for 80.7% of joint-treatment medication and therapy costs in the HA group. This difference mainly relates to the denominator, follow-up duration, scope of costs, and the healthcare delivery system.

Apart from HA use, age and number of comorbidities were associated with higher costs. Each additional year of age corresponded to 1.3% higher costs, and each additional comorbidity to 7.6% higher costs. HI coverage level was also associated with costs, but this may reflect differences in beneficiary groups and service use rather than the effect of the insurance policy itself.

This study has several limitations. First, the retrospective, single-hospital design limits the generalizability of the results to the whole Vietnamese population or the region. Second, the HA group was defined by recorded HA use at any time during the study period, so some visits of patients in the HA group may have occurred before the first HA injection. This grouping suits the aim of describing patients with and without recorded HA use, but it does not allow a temporal causal sequence to be established. Third, at this hospital, HA use is tied to an inpatient episode for the procedure, so medication use in the HA group is directly related to knee osteoarthritis, whereas inpatient stays in the non-HA group may arise from other diagnoses, leading to confounding by baseline patient characteristics. Although the model adjusted for observed characteristics, the data did not include Kellgren–Lawrence grade, BMI, pain severity, VAS, WOMAC, physical function, quality of life, or reasons for treatment choice, so a risk

of confounding by indication remains. Fourth, costs reflect only services recorded at Thong Nhat Hospital; services provided at other facilities, indirect costs, and direct non-medical costs were not observed. Finally, annualizing costs per person-year is a standardization over time and should not be interpreted as a forecast of individual costs for a full year [12].

5. CONCLUSION

Among 25,575 patients with knee osteoarthritis, 894 (3.5%) had recorded HA use. The HA group had lower proportions of visits with recorded NSAIDs and analgesics but a higher proportion with SYSADOAs than the non-HA group. In patients with at least 30 days of available observation, the median direct medical cost was VND 13.23 million/person-year in the HA group and VND 1.86 million/person-year in the non-HA group. After adjustment for observed characteristics, the HA group had a cost ratio of 4.833 (95% CI: 4.019–5.874). These results reflect differences in medication use patterns, care pathways, and costs between the two groups in hospital practice; they do not allow the conclusion that HA independently increases costs or provides greater clinical benefit.

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