#### ORIGINAL RESEARCH

# The Economic Burden of Patients with Diabetic Peripheral Neuropathic Pain Based on a Real-World Study in China

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**Objective:** Currently, there is no specific characterization of the economic burden of Diabetic Peripheral Neuropathic Pain (DPNP) in most Asian countries. The purpose of this study was to understand the economic burden of DPNP in China from a healthcare system perspective.

**Methods:** The analysis was conducted using the SuValue<sup>®</sup> database, a large electronic medical record (EMR) database which covers 182 hospitals across 22 provinces in China. A 12-month baseline and 12-month follow-up period were used to compare healthcare resource utilization and costs before and after the initial diagnosis of DPNP.

**Results:** A total of 7373 adult patients with DPNP were identified and 4220 (57.24%) patients were treated. Analgesics (n=2044, 48.44%) and anti-inflammatory drugs (n=1990, 47.16%) were the most used treatments. Among DPNP treated patients, the mean (SD) total all-cause healthcare costs during follow-up period were 8980.83 (17,721.48) CNY, with a 4446.48 CNY increase (p-value < 0.001) from 4534.35 (9791.93) CNY at baseline. The cost increase was primarily driven by an increase in hospitalization and medication costs after the DPNP diagnosis. A similar trend in the treatment pattern and total cost increase after DPNP diagnosis was also found in a sensitivity analysis when excluding over-the-counter (OTC) products from the analysis.

**Conclusion:** DPNP is associated with significantly increased utilization of healthcare services and costs for patients in China. **Keywords:** diabetic peripheral neuropathic pain, economic burden, healthcare resource utilization, cost

#### Introduction

Diabetes mellitus is one of the most common and costly diseases worldwide, the global prevalence of diabetes mellitus in 2011 was 366 million (8.3%), and this figure is also expected to rise to 552 million (9.9%) by 2030.<sup>1</sup> Diabetic peripheral neuropathy (DPN) is one of the most common neuropathic syndromes seen in patients with diabetes, and it could result in foot ulcers, infections, and nontraumatic amputation.<sup>2</sup> Globally, DPN affects 30–50% of patients with diabetes, and 40–60% of DPN patients experience diabetic peripheral neuropathy pain (DPNP).<sup>3–9</sup> In China, a study estimated the prevalence of DPNP was as high as 57.2% among patients with type 2 diabetes mellitus (T2DM) and DPN.<sup>10</sup>

The clinical symptoms of DPNP include pain of burning, shooting or aching type. It may also be accompanied by allodynia, hyperalgesia and numbness which often get worse at night that could result in disturbed sleep, anxiety and depression, and can have a profound effect on quality of life and loss of work productivity.<sup>11–16</sup> DPNP is associated with significant morbidity and mortality and increased health-related costs and is a very common cause of nontraumatic amputations and hospital admissions.<sup>17</sup>

Although the pathophysiology of DPNP is not clearly understood, there is a consensus that the toxic effects of hyperglycemia play an important role in the development of this complication.<sup>18</sup> Theories that have been proposed to explain the pain related to DPNP include changes in the blood vessels that supply the peripheral nerves, metabolic and

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437 repress.com/terms. autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channels expression, and more recently, the role of central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways.<sup>19</sup>

The diagnosis of DPNP involves a combination of assessing symptoms and history, conducting a neurological examination, and potentially performing confirmatory tests, with the goal of identifying the neuropathic origin of the pain and its impact on daily life.<sup>20,21</sup> And several guidelines exist for pharmacotherapy management in DPNP,<sup>6,17,22–24</sup> with recommending gabapentinoids (gabapentin, pregabalin), tricyclic antidepressants (TCA), and serotonin and nor-epinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine) as suitable first-line treatments, and other medications such as anti-inflammatory agents and opioids to alleviate pain. Yet the effectiveness of these treatments is difficult to ascertain,<sup>25–31</sup> and other challenges exist in the management of DPNP: the condition is often underdiagnosed and undertreated; achieving a complete resolution in pain is rare, with 30–50% reduction considered a good outcome; additionally, the medications used often have a significant side effect burden requiring careful consideration of comorbidities and contraindications.<sup>21</sup>

DPNP is associated with substantial economic burden,<sup>12–14</sup> and it together with other diabetic complications (eg coronary heart disease, nephropathy, retinopathy) contribute a significant part of the costs associated with diabetes.<sup>32–34</sup> A study with analysis of healthcare claims data in the United States reported that, the average total annual costs of patients with diabetes only was \$6632, while patients with DPNP, had much higher annual costs ranging from \$27,931 to \$30,755.<sup>14</sup> On the diabetes spectrum, it was shown that the high-income countries spent much more than the low-income countries on diabetes, suggesting more resources were required to provide basic diabetes care in low-income countries.<sup>33,35</sup>

There is limited literature available on current drug utilization patterns, healthcare utilization costs, and patient characteristics of patients with DPNP in China. To address these knowledge gaps, we conducted a retrospective observational study focusing on the Chinese DPNP population with the following objectives: 1) to describe the characteristics of newly diagnosed DPNP patients, 2) to assess the current treatment patterns for DPNP, and 3) to analyze healthcare resource utilization and costs of DPNP.

## Methodology

#### Objective

In this study, we aimed to characterize patients' profiles who were newly diagnosed with Diabetic Peripheral Neuropathic Pain (DPNP) in China. In addition, we describe the treatment patterns for DPNP, as well as quantify the healthcare resource utilization and costs of DPNP.

## **Database Source**

A retrospective analysis was conducted using the SuValue database, which is an electronic medical record (EMR) database covering over 100 million patients from 182 hospitals (21 Tier 3 hospitals, 114 Tier 2 hospitals, and 47 Tier 1 hospital) across 22 provinces in China. All raw data collected from hospitals were cleaned and de-identified before being transferred to the research database (final database), and medical history (diagnosis and prescription) was standardized using a standard coding system (ICD-9-CM/ICD-10-CM and ATC codes). The research-identifiable database reports demographic information including date of birth, gender, race/ethnicity, marital status, medical insurance type, and geographical region. The database also provides clinical information, such as comorbidity and health service information, including hospital tiers, inpatient stays, office visits, lab tests, and medical prescriptions. Medical cost information was also recorded in the database, including payments from health insurance organizations and out-of-pocket payments from patients.

## Study Population

To identify patients with DPNP, a search for inpatient admissions and physician visits with a diagnosis of DPNP was conducted using ICD diagnosis codes (ICD-10-CM: E11.40, ICD-9-CM: 357.2) or diagnosis descriptions entered by

physicians in the SuValue database. Additionally, patients diagnosed with both diabetes and neuralgia at the same visit were included as DPNP patients in the analysis.

For each patient, the date of the first DPNP diagnosis observed from January 1, 2013, to December 31, 2020, was defined as the index date. The baseline and follow-up periods were defined as 12 months before and after (including) the index date, respectively.

Patients with a diagnosis of DPNP in the baseline period or those without complete demographic, admission, or discharge information were excluded from the study, and patients were restricted to adults only (aged 18 years or older on the index date).

#### Study Measures

Demographic information, including age, gender, medical insurance type, and hospital type, was recorded for each patient on the index date. Key comorbidities were identified based on ICD-9-CM/ICD-10-CM codes recorded in both inpatient visits and outpatient visits during the baseline period. The Charlson Comorbidity Index (CCI) score was calculated to quantify the baseline clinical conditions, and CCI consists of 17 comorbidities, with comorbidities being weighted from 1 to 6 for mortality risk and disease severity, and then summed to form the total CCI score.<sup>36–38</sup>

DPNP-related prescriptions were captured in the database via ATC codes or generic names (<u>Supplemental Appendix 1</u> and <u>2</u>). Non-medication treatments for DPNP, such as physical therapy (PT) (for example, acupuncture and transcutaneous electric nerve stimulation), were also included in the analysis (<u>Supplemental Appendix 3</u>), and PT can help on improvement of DPNP symptoms including muscle weakness, pain, loss of balance, and lower limb dysfunction.<sup>39,40</sup> PT is commonly utilized within one month after a DPNP outpatient visit as a local standard practice based on our consultation with local experts. Therefore, we defined DPNP-related physical therapy as a PT encounter within one month following their DPNP outpatient visit, and such encounters were tracked over the follow-up period and included in the total cost and resource utilization.

The primary analysis included OTC products for treatment patterns and cost analysis. According to the local experts we consulted, as well as some literatures suggested, physicians in hospital prescribe and basic national health insurance covers designated OTC products in China.<sup>41</sup> The National Reimbursement Drug List (NRDL) includes information on price, brand, production factors, and listings of OTC products which can be reimbursed.<sup>42</sup> This list serves as an important component of the Chinese social medical insurance system and plays a significant role in balancing the prices in the OTC market. Therefore, it is necessary to include any OTC product listed on the NRDL for the treatment of DPNP to understand the full cost burden associated with the disease. Supplemental Appendix 2 provides a list of OTC products from the SuValue database.

Both healthcare resource utilization and costs associated with the disease were included as economic burden. Healthcare resource utilization was estimated using the number of visits for each healthcare resource category (outpatient, emergency room (ER), and inpatient) during the baseline and follow-up periods. Healthcare costs were assessed as the annualized all-cause costs during the baseline and follow-up periods. The total all-cause costs of a patient were the sum of inpatient, outpatient, and medication costs, and each was defined as follows:

- Outpatient costs include the total costs of physician visits such as laboratory tests, imaging, and registration costs.
- Inpatient costs are the sum of all itemized costs incurred during hospitalization such as nursing expenses, surgery costs, lab test costs, imaging costs, and registration costs.
- Medication costs were defined as the sum of any medication costs incurred during hospitalization or outpatient visits.

Moreover, incremental costs are defined as the difference in all-cause healthcare costs between the baseline and followup periods for DPNP patients, and such incremental costs were considered to be attributable to DPNP.

All-cause costs associated with DPNP are defined as incremental costs from the baseline to follow-up period in the following categories:

- Outpatient costs
- Inpatient costs
- Medication costs

## Study Analysis

A descriptive analysis was conducted on the variables of interest, including patient demographics, comorbidities, treatments, healthcare resource utilization, and costs. Descriptive statistics of continuous variables were summarized as mean, standard deviation, median, and lower and upper quartiles. Descriptive statistics of categorical variables were summarized by frequency and percentage. Missing values were excluded from the analysis.

For variable comparison between the baseline and follow-up periods, Wilcoxon signed-rank tests were performed for continuous variables, and chi-square tests were performed for categorical variables. P-values were reported for all tests. A sensitivity analysis was conducted by excluding OTC products from the treatment pattern and cost analysis.

# Results

#### Primary Analysis

A total of 7373 DPNP patients were identified in the database, 56.44% were females and the mean (SD) age was 62.64 (12.81) years, 60.25% had health insurance coverage, 22.34%, 69.01% and 8.65% were diagnosed at Tier 3, 2 and 1 hospitals, respectively; and mean (SD) CCI score was 3.41 (1.80). Among all DPNP patients, 4220 (57.24%) patients received treatment after diagnosis and the remaining 3153 (42.76%) patients were not treated. A flow chart was provided to describe patient selection in detail (Figure 1). Compared to untreated patients, treated DPNP patients were older [mean (SD) age (years) = 63.74 (12.56) vs 61.16 (12.99)] and had more females (57.75% vs 54.68%). Of the treated patients with DPNP, 65.95% had health insurance, whereas the insurance coverage for the untreated group was 52.62%. More treated DPNP patients had slightly lower CCI scores than untreated patients at baseline [mean (SD) = 3.36 (1.92) vs 3.41 (1.74)] (Table 1).

The most prescribed medications for patients with DPNP were analgesics (48.44%) and anti-inflammatory drugs (47.16%), followed by anticonvulsants (12.18%), anesthetics (5.28%), and antidepressants (0.76%). The most common physical treatments were acupuncture (16.02%) and transcutaneous electric nerve stimulation (9.38%), and 4.48% had near infrared ray and 2.63% was treated with low-level laser (Table 2).

When comparing healthcare resource utilization before and after DPNP diagnosis, we observed significant increases of inpatient, outpatient, and ER admissions for all DPNP patients (Table 3), and for the treated DPNP patients, only outpatient and ER admissions increased significantly after diagnosis while the increase of inpatient admissions was not



Figure I Inclusion and Exclusion Criteria.

Abbreviations: DPNP, Diabetic Peripheral Neuropathic Pain; N, number of patients.

 Table I Patient Demographics and CCI Scores of DPNP Patients at Baseline

Variable	All DPNP Patients	Treated DPNP Patients	Untreated DPNP Patients	P-value*
Number of Patients	7373	4220	3153	
Age				
Mean (SD)	62.64 (12.81)	63.74 (12.56)	61.16 (12.99)	<0.001
Lower Quartile	54	56	52	
Median	64	65	62	
Upper Quartile	72	73	71	
Gender (n, %)				
Male	3212 (43.56%)	1783 (42.25%)	1429 (45.32%)	0.009
Female	4161 (56.44%)	2437 (57.75%)	1724 (54.68%)	
Medical Insurance (n, %)				
Health Insurance	4442 (60.25%)	2783 (65.95%)	1659 (52.62%)	<0.001
Out of Pocket	2931 (39.75%)	1437 (34.05%)	1494 (47.38%)	
Hospital Tier (n, %)				
Level I	638 (8.65%)	382 (9.05%)	256 (8.12%)	<0.001
Level 2	5088 (69.01%)	2763 (65.47%)	2325 (73.74%)	
Level 3	1647 (22.34%)	1075 (25.47%)	572 (18.14%)	
ССІ				
Mean (SD)	3.41 (1.80)	3.36 (1.92)	3.41 (1.74)	0.0030
Lower Quartile	2	2	2	
Median	3	3	3	
Upper Quartile	4	4	4	

Notes: \*P-values were calculated from Wilcoxon Signed Rank Test for continuous variables or chi-square test for categorical variables. Abbreviations: CCI, Charlson Comorbidity Index; DPNP, Diabetic Peripheral Neuropathic Pain; SD, standard deviation; n, number of patients.

Treatment	Treated DPNP Patients (N=4220)
Medications (n, %)	
Anti-depressants	32 (0.76%)
Anticonvulsants	514 (12.18%)
Analgesics	2044 (48.44%)
Anesthetics	223 (5.28%)
Anti-inflammatories	1990 (47.16%)

Table 2 Treatment Patterns of Treated DPNP Patients

(Continued)

Treatment	Treated DPNP Patients (N=4220)
Physical Treatment (n, %)	
Acupuncture	676 (16.02%)
Near Infrared Ray	189 (4.48%)
Low-Level Laser	111 (2.63%)
Transcutaneous Electric Nerve Stimulation	396 (9.38%)
Operation (n, %)	
Avulsion of Trigeminal Nerve	3 (0.07%)
Other Treatment (n, %)	
Nerve Block Therapy	17 (0.40%)

Table 2 (Continued).

Abbreviations: DPNP, Diabetic Peripheral Neuropathic Pain; N, number of patients; n, number of patients.

Table 3 All-Cause Healthca	re Resource Utilizatio	on of All DPNP Patients
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HRU, Mean (SD)	Baseline (N=7373)	Follow Up (N=7373)	P-value*
Inpatient Admissions	0.37 (0.98)	0.56 (1.08)	0.011
Outpatient Admissions	13.56 (17.56)	13.57 (17.73)	<0.001
ER Admissions	1.08 (4.77)	1.18 (5.30)	<0.001

Notes: \*P-values were calculated from Wilcoxon Signed Rank Test for continuous variables or chisquare test for categorical variables.

Abbreviations: DPNP, Diabetic Peripheral Neuropathic Pain; HRU, healthcare resource utilization; SD, standard deviation; N, number of patients; ER, emergency room.

statistically significant (Table 4). The total cost increase trend from the baseline to follow-up period was observed among all DPNP patients, from a mean (SD) of 4112.94 (8653.96) CNY to 7489.36 (14,782.68) CNY since DPNP diagnosis (Tables 5). Among the treated DPNP patients, the mean (SD) total costs were 4534.35 (9791.93) CNY in the baseline period and 8980.83 (17,721.48) CNY in the follow-up period, with a significant increase of 4446.48 CNY (p-value < 0.001), and the total cost increase was mostly due to the increase in inpatient and medication costs (Tables 6). The significant increase in healthcare resource utilization and costs indicates that the diagnosis of DPNP was followed by an increased health and economic burden on DPNP patients in China.

Table 4 All-Cause Healthcare Resource Utilization of Treated DPNP Patients

HRU, Mean (SD)	Baseline (N=4220)	Follow Up (N=4220)	P-value*
Inpatient Admissions	0.50 (1.11)	0.73 (1.18)	0.631
Outpatient Admissions	12.81 (17.80)	12.48 (17.52)	<0.001
ER Admissions	1.10 (5.21)	1.18 (5.26)	<0.001

Notes: \*P-values were calculated from Wilcoxon Signed Rank Test for continuous variables or chisquare test for categorical variables.

**Abbreviations**: DPNP, Diabetic Peripheral Neuropathic Pain; HRU, healthcare resource utilization; SD, standard deviation; N, number of patients; ER, emergency room.

Cost (CNY), Mean (SD)	Baseline (N=7373)	Follow Up (N=7373)	P-Value*
Total Costs	4112.94 (8653.96)	7489.36 (14,782.68)	<0.001
Outpatient Costs	451.96 (2195.83)	574.85 (2584.07)	<0.001
Inpatient Costs	1218.29 (4957.73)	2991.45 (9843.34)	<0.001
Medication Costs	2442.69 (4288.13)	3923.07 (5798.52)	<0.001

 Table 5 All-Cause Costs of All DPNP Patients

**Notes:** \*P-values were calculated from Wilcoxon Signed Rank Test for continuous variables or chi-square test for categorical variables.

**Abbreviations**: DPNP, Diabetic Peripheral Neuropathic Pain; CNY, Chinese Yuan; SD, standard deviation; N, number of patients.

Table 6 All-Cause Costs of Treated DPNP Patients

Cost (CNY), Mean (SD)	Baseline (N=4220)	Follow Up (N=4220)	P-value*
Total Costs	4534.35 (9791.93)	8980.83 (17,721.48)	<0.001
Outpatient Costs	368.28 (1096.33)	497.32 (1330.44)	<0.001
Inpatient Costs	1679.35 (5987.29)	4175.17 (12,208.31)	<0.001
Medication Costs	2486.73 (4728.01)	4308.34 (6671.13)	<0.001

Notes: \*P-values were calculated from Wilcoxon Signed Rank Test for continuous variables or chi-square test for categorical variables.

**Abbreviations**: DPNP: Diabetic Peripheral Neuropathic Pain; CNY: Chinese Yuan; SD: standard deviation; N: number of patients.

#### Sensitivity Analysis

A sensitivity analysis was conducted by excluding OTC products from medications to assess the impact of OTC products on comparisons between treated and untreated patients with DPNP. In the sensitivity analysis, patients who received only OTC products were considered untreated. Among 7373 patients with DPNP, 1619 (21.96%) were treated and 5754 (78.04%) were untreated (<u>Supplemental Figure 1</u>). When compared to the untreated patients, it was similar to the primary analysis that, the treated DPNP patients were older [mean (SD) age (year) = 64.01 (13.10) vs 62.25 (12.70)], with more covered by health insurance (65.60% vs 58.74%) and had more DPNP diagnosed at Tier 3 hospitals (26.31% vs 21.22%). However, the gender distribution and CCI scores at baseline were not significantly different between treated and untreated DPNP patients. (Supplemental Table 1).

With disregarding all anti-inflammatories and OTC analgesics as DPNP treatment, the most prescribed medications were analgesics (30.33%) followed by anticonvulsants (28.23%), antidepressants (1.61%), and anesthetics (0.62%). The most common physical treatments were acupuncture (41.63%) and transcutaneous electric nerve stimulation (24.46%) (Supplemental Table 2).

For the treated DPNP patients, only outpatient admissions increased significantly after DPNP diagnosis, while the increase in inpatient and ER admissions was not statistically significant (Supplemental Table 3), with a mean (SD) of total costs of 6216.12 (13,461.27) CNY in the baseline period and 12,304.69 (24,754.14) CNY in the follow-up period, with a significant increase of 6088.57 CNY (p-value < 0.001), which was mostly due to the increases in inpatient and medication costs (Supplemental Table 4).

Similar to the primary analysis, the sensitivity analysis showed deviations in patient characteristics, such as age and insurance coverage, between treated and untreated DPNP patients. Patients with DPNP were mostly treated with analgesics and anticonvulsants, together with OTC medications, including all anti-inflammatory drugs and some analgesics. Both analyses showed significantly increased costs after DPNP diagnosis, mostly because of inpatient and medication costs.

#### Discussion

Several studies have been conducted to quantify the health and economic burden of DPNP patients in other Asian countries,<sup>43,44</sup> and we believe that this is the first study on economic burden of DPNP patients in China.

In this study, we described the patient characteristics of newly diagnosed DPNP patients, summarized current treatment patterns for DPNP, and analyzed healthcare resource utilization and costs before and after DPNP diagnosis for all DPNP patients and those received treatment.

We observed that more women had DPNP than men, and the finding was consistent with previous studies that neuropathic pain was more often and more intense in females with diabetes.<sup>45,46</sup>

From a Chinese healthcare system perspective, this study revealed a significant economic burden associated with DPNP, most of which was due to increased hospitalization and medication costs after DPNP diagnosis. Another study in Japan reached similar conclusion by showing that DPNP patients had higher medical and medication costs than other DPN patients without painful symptoms.<sup>43</sup> When considering the broader DPN spectrum, a more recent observational cross-sectional study in China evaluated the cost and quantity of anti-diabetic drugs needed by patients with or without DPN, and it showed that the total annual cost of medication was higher for DPN patients than for non-DPN patients.<sup>47</sup>

This study showed a broad use of analgesics and anti-inflammatory drugs as the primary treatments of choice for DPNP in China, and in the sensitivity analysis with all OTC medications excluded, we observed the common use of physical treatments such as acupuncture (41.63%) and transcutaneous electric nerve stimulation (24.46%), they both indicated a lack of available targeted therapy, and such a lack of therapy may contribute to the burden.

This study has some limitations. Healthcare resource utilization (HRU) and cost were estimated for all-cause, but DPNP-specific, and our results for HRU and cost increase may be partially attributable to non-DPNP-related factors. Due to the cross-sectional study design with fixed one year before and after DPNP diagnosis for HRU and costs comparison, the longer-term economic impact was not captured. In addition, the SuValue database covered mostly on Tier 2 and Tier 1 hospitals in China, thus the results may not be representative of urban areas of China which has a higher concentration of Tier 3 hospitals than rural areas.

#### Conclusion

This cross-sectional study analyzed healthcare resource utilization and costs before and after DPNP diagnosis for all DPNP patients and those received treatment, based on a large EMR database in China. We found that DPNP is associated with significantly increased utilization of healthcare services and costs, mostly attributed to more hospitalization and medication costs after DPNP diagnosis. Our findings will provide more insights about the economic burden of DPNP patients in China, and the introduction of clinical practice guidelines for the treatment of DPNP could lead to more directed therapy to reduce the health and economic burden.

#### **Ethics Statement**

In accordance with Item 1 and Item 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, this study is exempt from ethical approval.

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#### Disclosure

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