OPEN ACCESS

Global estimates of prevalence of chronic painful neuropathy among patients with chemotherapy-induced peripheral neuropathy: systematic review and meta-analysis of data from 28 countries, 2000–24

Ryan S D'Souza ,[1] Chandan Saini,[2] Nasir Hussain ,[3] Saba Javed ,[4] Larry Prokop,[5] Yeng F Her[1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rapm-2024-106229).

[1]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, New York, USA
[2]Department of Rehabilitation Medicine, Rush University Medical Center, Chicago, Illinois, USA
[3]Ohio State University, Columbus, Ohio, USA
[4]University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[5]Mayo Clinic Libraries, Mayo Clinic Minnesota, Rochester, Minnesota, USA

Correspondence to
Dr Ryan S D'Souza;
DSouza.Ryan@mayo.edu

Received 11 November 2024
Accepted 5 December 2024

To cite: D'Souza RS, Saini C, Hussain N, *et al*. *Reg Anesth Pain Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/rapm-2024-106229

ABSTRACT

Introduction Although the prevalence of chemotherapy-induced peripheral neuropathy (CIPN) has been reported, the proportion of patients with CIPN who report chronic painful neuropathy remains poorly understood, despite its significant impact on patients' quality of life and treatment outcomes.

Methods A systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary outcome was the pooled prevalence of chronic (≥3 months) painful CIPN among patients diagnosed with CIPN. Estimates from each study were transformed using double arcsine transformation and pooled in a meta-analysis using an inverse variance heterogeneity model. Subgroup analysis was conducted based on geographical region, sex, chemotherapy regimen, primary cancer type, and funding source; meta-regression analysis was conducted based on study design, human development index (HDI), and publication year.

Results 77 studies from 28 countries, encompassing 10 962 patients with CIPN, were included. Among patients diagnosed with CIPN, the pooled prevalence of those reporting chronic painful CIPN was estimated at 41.22% (95% CI 32.40 to 50.19; 95% prediction interval 23.71 to 61.28). Substantial heterogeneity was observed across studies (I^2=95.27%; 95% CI for I^2 94.58 to 95.86). Subgroup analysis revealed that patients treated with platinum based agents and taxanes had the highest prevalence of chronic painful CIPN (40.44% and 38.35%, respectively), and among primary cancers, those with lung cancer reported the highest prevalence of chronic painful CIPN (60.26%). Study design, HDI, and publication year were non-significant moderators of prevalence estimates. Based on our GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment, the certainty of evidence was considered very low.

Conclusion This study provides the first comprehensive global estimate of the prevalence of chronic painful CIPN, highlighting its significant burden on patients worldwide. The variation in prevalence across geographical regions, chemotherapy regimens, and primary cancers underscores the need for tailored pain management strategies and further research to address potential disparities.

Trial registration PROSPERO CRD42024579459.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chemotherapy-induced peripheral neuropathy (CIPN) is a common complication of cancer treatment, but the global prevalence of painful CIPN and its variability based on select sociodemographic, clinical, and methodological factors remain poorly understood.

WHAT THIS STUDY ADDS

⇒ This study provides the first comprehensive global estimate of chronic painful CIPN prevalence, revealing substantial heterogeneity influenced by chemotherapy type, primary cancer, and geographic region.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By quantifying the global burden of chronic painful CIPN, this study highlights the need for targeted preventive strategies, personalized management approaches, and equitable access to care to mitigate its impact worldwide.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition that occurs from administration of neurotoxic chemotherapeutic drugs. CIPN often manifests with motor and sensory disturbances, including hypoesthesia, paresthesia, and dysesthesia in a symmetric, stocking glove distribution.[1] The occurrence and severity of CIPN are impacted by multiple factors, such as chemotherapeutic drug type, cumulative dose, and patient-related factors (eg, pre-existing neuropathy and use of other neurotoxic drugs). While a substantial portion of patients with CIPN predominantly experience non-painful neuropathic features (eg, numbness or tingling only), those with accompanying painful neuropathy are likely to endure a higher burden and diminished quality of life. Studies have highlighted that painful CIPN is associated with significant functional impairment and contributes substantially to the economic burden on healthcare systems, with increased disability costs and a heightened need for pain management interventions.[2] The persistence of severe and painful CIPN can also

lead to dose reductions or discontinuation of chemotherapy, adversely affecting overall prognosis and cancer-related mortality.[3]

Despite the clinical significance of painful CIPN, its pathophysiology remains incompletely understood. The condition may likely arise from direct neurotoxic effects on peripheral nerves, including mitochondrial damage, ion channel dysfunction, and neuroinflammation, that disrupt normal nerve signaling and lead to persistent pain.[4] The American Society of Clinical Oncology guideline highlights the complexity of managing painful CIPN, noting the limited efficacy of current pharmacological treatments, such as duloxetine, and the lack of preventive strategies.[5 6] Patients typically require a multimodal approach consisting of conservative management, oral analgesics for neuropathic pain, and interventional procedures (eg, neuromodulation and intrathecal drug delivery).[6–9] Despite these treatments, severe and intractable cases occur, necessitating last resort measures, such as discontinuation of chemotherapy.

Studies have approximated that 70% of patients experience CIPN within the first month of receiving chemotherapy, followed by 60% at 3 months, and 30% at 6 months or later.[10] Rates of CIPN vary, with higher rates observed in those treated with platinum-based drugs, taxanes, and vinca alkaloids.[10] However, the prevalence of painful CIPN remains unknown and, to the best of our knowledge, no previous systematic reviews with meta-analysis exist on this topic. It is possible that the prevalence of painful neuropathy among various subpopulations with CIPN may vary widely, influenced by factors such as the specific chemotherapeutic agents used, duration of treatment, and time elapsed since chemotherapy completion.

Given the projected increase in cancer survivorship and the rising incidence of CIPN due to more aggressive chemotherapy regimens, understanding the global prevalence of chronic painful neuropathy in CIPN is critical. Understanding the prevalence of painful CIPN is also an important step in improving early detection and treatment, and addressing its widespread socioeconomic impact. It is critical to assess the prevalence of painful CIPN by demographics, geographic region, financial status, and other factors to address health inequalities globally. Thus, it is a priority in cancer-related epidemiological research to benchmark the prevalence of painful CIPN for past and future comparisons.

In this study, our aim was to address this existing knowledge gap by evaluating the global prevalence of chronic painful CIPN, based on literature published from 2000 to 2024. Also, in this meta-analysis, we explored potential moderators that may account for heterogeneity in the prevalence estimates, including sociodemographic factors (sex, economic metrics), clinical factors (chemotherapy regimen, primary cancer), and methodological factors (study design, funding source, publication year). We hypothesized that the chemotherapy regimen and reporting practices over time will significantly influence the reported prevalence of painful CIPN. Detailed knowledge about the prevalence of chronic neuropathic pain in CIPN could facilitate accurate deployment of pain therapies based on the rate of anticipated need.

MATERIALS AND METHODS

We performed a meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines,[11] and guidelines for publishing systematic reviews and meta-analyses in pain medicine.[12–15]

Search strategy

A search strategy was developed in collaboration between the principal investigator (RSD) and a medical librarian experienced in systematic review and meta-analysis methodology (LP). The medical librarian (LP) conducted the database searches. A comprehensive search was performed on August 13, 2024, identifying relevant studies that reported the occurrence of chronic painful CIPN among a population of patients with CIPN. There were no date or language restrictions. We searched electronic databases including Ovid Medline and Epub Ahead of Print, Ovid Embase, Web of Science, and Scopus. A controlled vocabulary supplemented with keywords was used. The complete search strategy is described in online supplemental eTable 1.

Study selection

Original publications were considered for inclusion in this meta-analysis based on the following criteria:

1. studies of any design (randomized clinical trials (RCTs), observational studies, and case series) including abstracts and unpublished articles. For case series, we only included this article type if data were reported on at least 10 patients who received chemotherapy (*a priori* decision)
2. studies that reported the prevalence of chronic painful CIPN among a cohort of adult patients (aged ≥18 years) with CIPN, or reported the relevant data (eg, number of cases of chronic painful CIPN and total number of patients with CIPN) to calculate the prevalence. The time duration of pain necessary to classify as chronic pain was defined as ≥3 months[16]
3. to facilitate a comprehensive capture of studies, we did not mandate for painful CIPN prevalence to be the primary outcome in included articles.

Studies were excluded if they met the following criteria: conference abstracts; studies that were not available in English; case series that included <10 patients who received chemotherapy; studies that evaluated treatment outcomes for CIPN and painful CIPN; studies that were based on children and adolescents; and studies that reported painful CIPN that occurred for <3 months.

Study screening

All titles and abstracts were independently screened by two authors (CS and YFH) using the Covidence online software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). The full text versions of all eligible citations were independently reviewed by two reviewers for final inclusion (CS and YFH). Any discrepancies were adjudicated by another independent author (RSD).

Data extraction

Data were extracted into an excel spreadsheet (Microsoft Excel 2016) by two independent reviewers (CS and YFH) with any disagreements resolved by a third reviewer (RSD). The following data were extracted: total number of patients diagnosed with CIPN, total number of patients with chronic (≥3 months) painful CIPN, country, continent, sex of patients, drug class(es) of chemotherapy regimen, primary cancer diagnosis, anatomical location of CIPN (upper extremities, lower extremities, both), study design (RCT, prospective observational study, retrospective observational study, case series), socioeconomic status of country according to the human development index (HDI), funding source, and year of publication. HDI is a composite metric consisting of variables that measure life expectancy, income per capita, and education.[17] Each component is

normalized on a scale that ranges between 0 and 1, and then the geometric mean is calculated to derive the composite score (0–1). A score of >0.800 signifies a very high HDI, 0.700–0.799 signifies a high HDI, 0.550–0.699 signifies a medium HDI, and <0.550 signifies a low HDI.

Outcomes of interest, subgroup analysis, and meta-regression

The primary outcome was the pooled prevalence of chronic painful CIPN (defined as ≥3 months since CIPN onset) among patients diagnosed with CIPN. The authors performed meta-regression analysis to determine if certain covariates may moderate and contribute to the heterogeneity or observed variations between studies. Specifically, meta-regression analysis was only performed for continuous variables (eg, HDI, year of publication) and for categorical variables (eg, study design) if there were at least 10 studies per covariate. Subgroup analysis of chronic painful CIPN prevalence was performed for the remaining variables based on country, continent, sex (excluding studies that focused on female-only cancers, such as ovarian cancer), chemotherapy regimen, type of primary cancer, and funding source. Subgroups with at least two study entries were included in the subgroup analysis. An exception to this was made for the subgroup analysis based on country in order to provide granular and comprehensive data for all included countries. We did not contact the authors of the included studies for missing data. We did not perform any adjustments for multiple comparisons because these additional analyses were considered exploratory.

Statistical analysis

We recorded the total number of cases of chronic painful CIPN and total sample size of patients with any CIPN. We performed a meta-analysis to obtain a pooled estimate of prevalence of chronic painful CIPN with 95% CIs using MetaXL software 5.3 (EpiGear International, Queensland, Australia). Estimates from each study were transformed using the Freeman–Tukey transformation (double arcsine transformation). We chose this transformation for two reasons: (1) to address the issue of confidence intervals laying outside of 0–100%; and (2) to address variance instability by minimizing the influence of studies with extreme prevalence estimates (eg, 0 or 100%) on the pooled estimate.[18] The transformed point estimates (95% CI) were pooled in a meta-analysis using an inverse variance heterogeneity model because this model has been shown to provide better coverage probabilities for 95% CI than the random effects model.[19 20] We also calculated and reported the 95% prediction interval for the pooled prevalence estimate. Additionally, a cumulative meta-analysis was conducted to explore how prevalence estimates evolved over time. Statistical significance was set at <0.05.

Meta-regression analysis was conducted in IBM SPSS Statistics for Windows, V.29.0 (IBM, Armonk, New York, USA). Consistent with the primary outcome analysis, we used the inverse variance heterogeneity model and associated weights for the meta-regression analysis. We used robust standard errors in the meta-regression model, which generates standard errors for heterogeneous data that are typically heteroskedastic. This was executed in SPSS by using the HC1 function, which is a degrees-of-freedom adjustment, to incorporate robust standard errors.

Appraisal of bias, quality, and certainty in prevalence estimates

We assessed publication bias (eg, small study effects) using the Doi plot and LFK index, which can detect and quantify asymmetry.[21] LFK values beyond ±1 indicate asymmetry. Statistical heterogeneity was determined using the I^2 statistic (and 95% CI for the I^2 statistic), with a cut-off of 75% indicating substantial heterogeneity.

Risk of bias was assessed using a tool[22] consisting of four questions that has been used in previous prevalence meta-analyses.[23] Two reviewers (YFH and CS) assessed if each study satisfied each of the following four questions, which related to selection, ascertainment of exposure, ascertainment of outcome, and reporting; discrepancies were adjudicated by consensus or by a third reviewer (RSD).

1. Do(es) the patient(s) represent the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
2. Was the exposure (chemotherapy) adequately ascertained?
3. Was the outcome (chronic pain) adequately ascertained?
4. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

The certainty of prevalence estimates for the primary outcome was assessed following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework.[24] This assessment considered several domains: risk of bias, inconsistency, indirectness, publication bias, and imprecision. Based on these criteria, the overall certainty was categorized as high (indicating that further research is unlikely to alter confidence in the estimate), moderate (suggesting that additional research may influence confidence in the estimate and may potentially modify the estimate), low (indicating a high likelihood that further research will impact confidence and alter the estimate), or very low (reflecting considerable uncertainty in the estimate). Evaluation procedures of GRADE domains paralleled those used for assessing risk of bias.

Protocol amendments

The statistical model was adjusted from a random effects model to an inverse variance heterogeneity model to improve coverage probabilities for 95% CIs. Subgroup analyses were also adapted to meta-regression analyses when at least 10 studies were available per subgroup. Additionally, each study underwent a risk of bias assessment to enable a thorough evaluation of bias risk and to support a more detailed GRADE certainty assessment (specifically, the risk of bias domain). A cumulative meta-analysis was incorporated to provide an alternative approach for analyzing changes in effect size over time. Finally, subgroup analyses were conducted for sex and funding source, as these factors are frequently moderators of effect size.

RESULTS

Identification of studies

The study selection is presented in the PRISMA diagram (figure 1). The initial search gave 525 unique studies. Of these, 145 full text articles were obtained for further screening of the entire article, of which 68 were excluded. Reasons for exclusion of studies after full text review are included in online supplemental eTable 2. A total of 77 articles published between 2000 and 2024 were included in the final analysis, comprising a total of 10 962 participants with CIPN worldwide (28 countries), of which 4545 had painful CIPN.

Study characteristics

Key characteristics of each study are reported in online supplemental eTable 3. Studies were conducted across 28 countries,

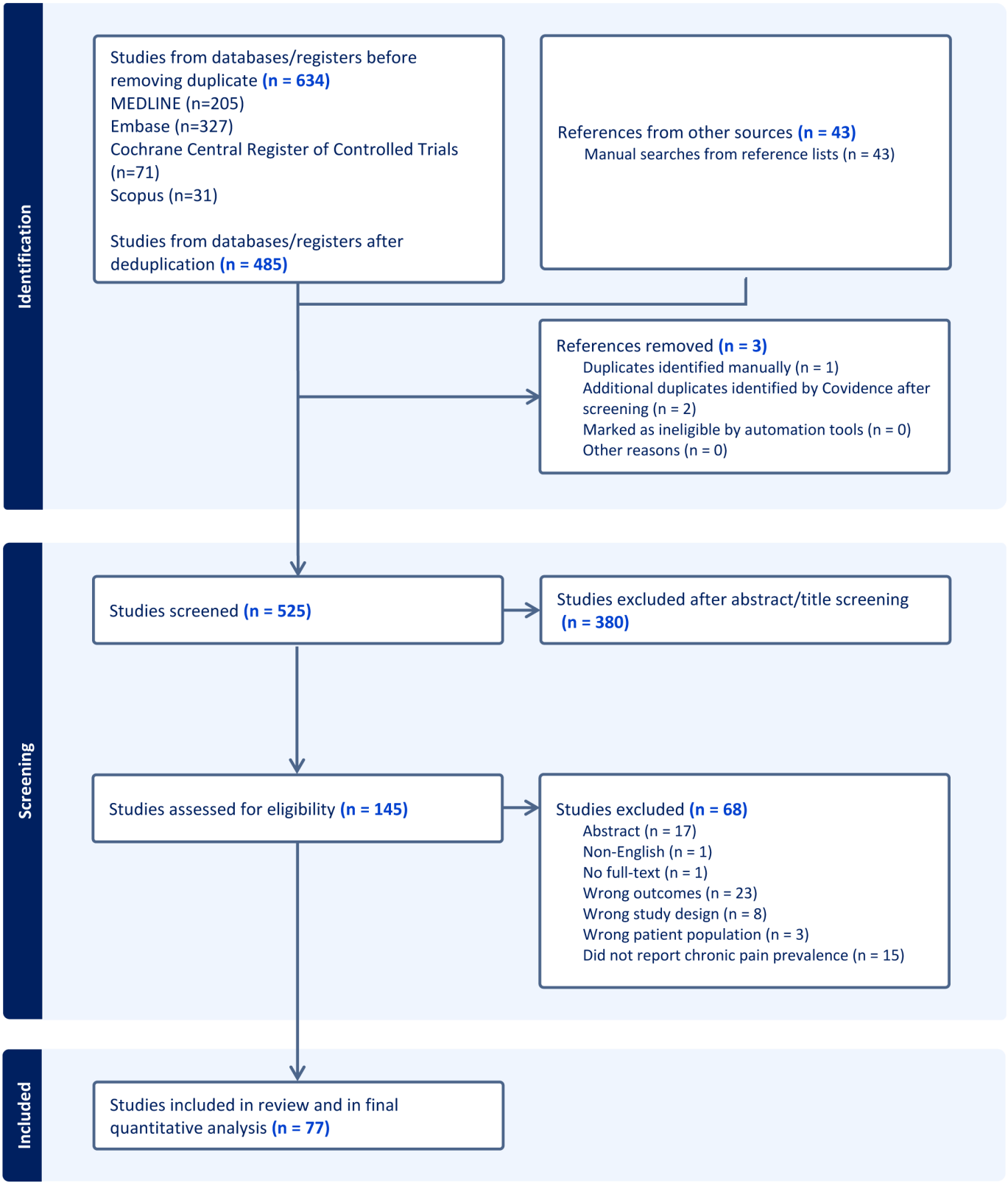

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. Flowchart demonstrates the study selection process.

with the highest number conducted in the US (13 studies, 16.88%) and Japan (10 studies, 13.00%). Most studies were prospective observational studies (35 studies, 45.45%), followed by 29 retrospective observational studies (37.66%) and 13 RCTs (16.88%). The funding sources of studies were highly variable, with institutional funding only (10 studies, 12.99%), industry funding only (10 studies, 12.99%), and institutional plus government funding (nine studies, 11.69%) representing the most common sources. Sample sizes ranged from 7 to 1760 patients (median 61). Among the five studies that provided non-aggregate

data on sex, there were 216 women and 227 men. Notably, most studies either reported all patients in aggregate without specifying sex or focused predominantly on specific cancers in women (eg, ovarian, endometrial cancer).

In terms of the primary cancer type, the highest number of studies focused on colorectal cancer (25 studies, 32.47%) and breast cancer (17 studies, 22.08%). A total of 14 studies (18.18%) included patients with different primary cancer types. Most studies (63 studies, 81.82%) reported patients with CIPN in the upper and/or lower extremity. In terms of the chemotherapy regimen, the highest number of studies focused on patients who received platinum-based agents in 13 studies (16.88%), followed by taxanes in 11 studies (14.28%), platinum-based agents plus taxanes in six studies (7.79%), and folinic acid, fluorouracil, and oxaliplatin (FOLFOX) in five studies (6.49%). A substantial portion of studies reported data on patients who received multiple and different classes of chemotherapy agents. In terms of HDI, there were 67 studies (87.01%) conducted in countries with very high HDI, nine studies (11.69%) conducted in countries with high HDI, and one study (1.30%) conducted in a country with low HDI.

Outcomes of interest and subgroup analysis

Of patients diagnosed with CIPN, the pooled prevalence estimate of those with chronic painful CIPN from 77 studies (n=10 962) was 41.22% (95% CI 32.40 to 50.19; 95% prediction interval 23.71 to 61.28) with evidence for substantial between study heterogeneity (I^2=95%; 95% CI for I^2 94.58 to 95.86, p<0.01; figure 2). Prevalence rates based on country are shown in online supplemental eFigure 1, although meaningful subgroup analysis was unable to be performed as many countries were represented by one or two studies. The prevalence of chronic painful CIPN varied based on various analyzed subgroups (online supplemental

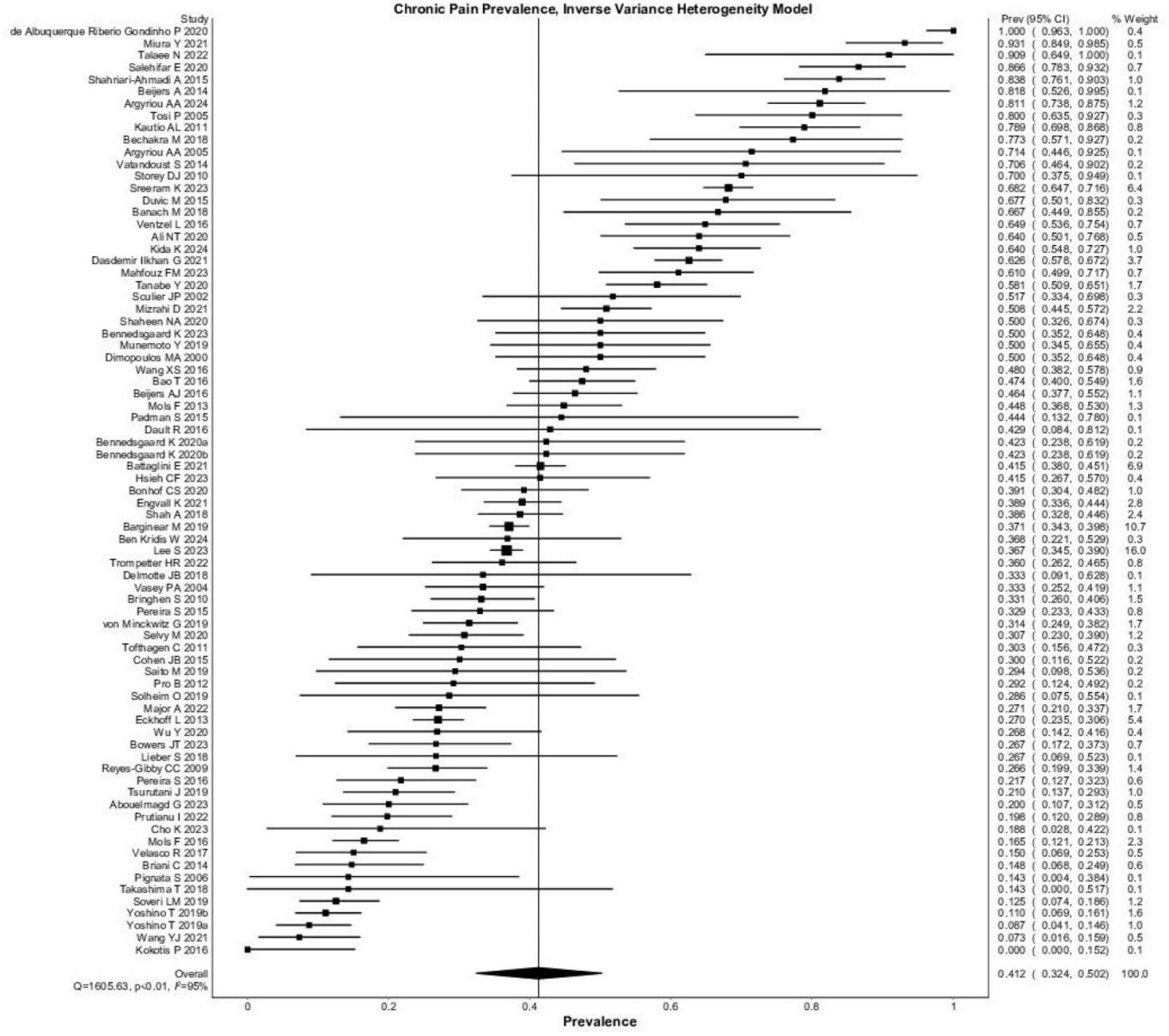

Figure 2 Forest plot showing proportion of chronic painful chemotherapy induced peripheral neuropathy (CIPN) among patients with CIPN. The forest plot shows transformed prevalence estimates with 95% CIs from each study, and reports the aggregate global prevalence of chronic painful CIPN among those with CIPN using an inverse variance heterogeneity model.

eFigures 2–6). However, despite these subgroup analyses, statistical heterogeneity persisted within each subgroup.

When prevalence rates were stratified by continent (online supplemental eFigure 2), studies that took place in Asia reported the highest prevalence of chronic painful CIPN (46.52%; 95% CI 26.35 to 66.99), while studies that took place in Europe reported the lowest prevalence of chronic painful CIPN (35.92%; 95% CI 26.53 to 45.58); there were no statistically significant differences between analyzed subgroups. When subgroup analysis was performed based on sex (online supplemental eFigure 3), there were similar prevalence rates of chronic painful CIPN in women (75.31%; 95% CI 52.28 to 94.84) and men (70.94%; 95% CI 43.23 to 94.71).

In terms of chemotherapy regimen (online supplemental eFigure 4), studies with data on patients who received platinum-based agents (40.44%; 95% CI 4.48 to 80.35) and taxanes (38.35%; 95% CI 22.78 to 54.54) reported the highest prevalence of chronic painful CIPN, while those with data on patients who received FOLFOX reported the lowest prevalence of chronic painful CIPN (16.43%, 95% CI 6.93 to 27.19); there were no statistically significant differences between analyzed subgroups. The following chemotherapy regimens were omitted from subgroup analysis because only one study reported rates of chronic painful CIPN with these regimens: bortezomib, bortezomib plus an immunomodulatory drug (eg, thalidomide), eribulin, 5-fluorouracil plus leucovorin plus oxaliplatin, FOLFOX plus epidermal growth factor antibody, immunomodulatory drug alone (eg, thalidomide alone), platinum plus capecitabine, and vinca alkaloid.

In terms of primary cancer (online supplemental eFigure 5), studies with data on patients with lung cancer reported the highest prevalence of chronic painful CIPN (60.26%; 95% CI 26.19 to 91.58), while those with data on patients with ovarian cancer (31.40%, 95% CI 23.91 to 39.15) and lymphoma (35.98%, 95% CI 15.33 to 58.07) reported the lowest prevalence of chronic painful CIPN; there were no statistically significant differences between analyzed subgroups. Endometrial cancer was omitted from subgroup analysis because only one study reported rates of chronic painful CIPN with this primary cancer.

In terms of funding source (online supplemental eFigure 6), studies with institutional funding reported the highest prevalence of chronic painful CIPN (51.25%; 95% CI 24.71 to 77.60), while those with extramural society funding (22.22%; 95% CI 4.00 to 44.01) reported the lowest prevalence of chronic painful CIPN; there were no statistically significant differences between analyzed subgroups. Regarding the anatomical location of chronic painful CIPN, a subgroup analysis was not feasible due to inadequate number of studies in certain subgroups (eg, upper extremity symptoms only).

Meta-regression analysis

Overall, the meta-regression model based on study design did not explain the proportion of variance among individual studies (p=0.057; adjusted R^2=0.049; online supplemental eTable 1 and eFigure 7). The following reported p values were associated with corresponding coefficient hypothesis tests. Compared with the reference group (retrospective observational study), studies with an RCT study design reported lower overall chronic painful CIPN prevalence (β=−0.379, 95% CI −0.685 to −0.074, t=2.476, p=0.016), whereas the prospective observational study design was a non-significant moderator (β=−0.041, 95% CI −0.296 to 0.213, t=0.747, p=0.747).

HDI was a non-significant moderator (β=−1.185, 95% CI −2.813 to 0.443, t=−1.450, p=0.151) for overall chronic painful CIPN prevalence (online supplemental eTable 4 and eFigure 8). Similarly, publication year was a non-significant moderator (B=0.014, 95% CI −0.006 to 0.034, t=1.421, p=0.159) for chronic painful CIPN prevalence (online supplemental eTable 4 and eFigure 9). A forest plot displaying a cumulative meta-analysis with studies arranged sequentially based on publication date is shown in figure 3.

Risk of bias assessment

The doi plot and LFK index of the primary outcome indicated no asymmetry in effect size, indicating low likelihood of small study effects (LFK index=0.92; online supplemental eFigure 10). Risk of bias assessment across four domains (selection, ascertainment of exposure, ascertainment of outcome, and reporting) is displayed in online supplemental eTable 5. A common source of bias was ascertainment of outcome in 28.57% (n=22) of studies and ascertainment of exposure in 3.90% (n=3) of studies.

Certainty of prevalence estimates

Table 1 summarizes quality assessment according to the GRADE criteria for the primary outcome. The certainty in the estimate of chronic painful CIPN was judged to be very low due to inconsistency (statistical heterogeneity and methodological heterogeneity) and imprecision (wide 95% CI and 95% prediction interval). We decided not to downgrade certainty based on publication bias due to the variety of included study designs as well as the LFK index indicating no asymmetry.

DISCUSSION

Overall findings

Our study revealed that among patients diagnosed with CIPN, the pooled prevalence of chronic painful CIPN, derived from 77 studies encompassing 10 962 patients and 28 countries, was estimated at 41.22%. However, this finding is characterized by high statistical heterogeneity and very low certainty according to the GRADE criteria. When analyzed by continent, studies from Asia had the highest prevalence of chronic painful CIPN at 46.52%, while those from Europe reported the lowest prevalence at 35.92%. Patients treated with platinum-based agents and taxanes exhibited the highest prevalence of chronic painful CIPN at 40.44% and 38.35%, respectively. In terms of primary cancer, studies describing patients with primary lung cancer reported the highest prevalence at 62.26%, while those involving ovarian cancer and lymphoma reported the lowest prevalence at 31.40% and 35.98%, respectively. Meta-regression analysis showed that study design, HDI, and publication year did not significantly moderate the prevalence of chronic painful CIPN. Further, cumulative meta-analysis, ranked by year, demonstrated that results did not differ over time from the final pooled prevalence estimate.

Implications for clinical practice

Understanding the prevalence and predictors of chronic painful CIPN is critical for promoting early diagnosis and developing personalized treatment strategies. Our findings emphasize that chronic painful CIPN represents a substantial global health challenge, affecting more than 40% of those diagnosed with CIPN. The observed variations in prevalence across countries and continents may be attributed to factors such as genetic predisposition, socioeconomic status, quality of healthcare, availability

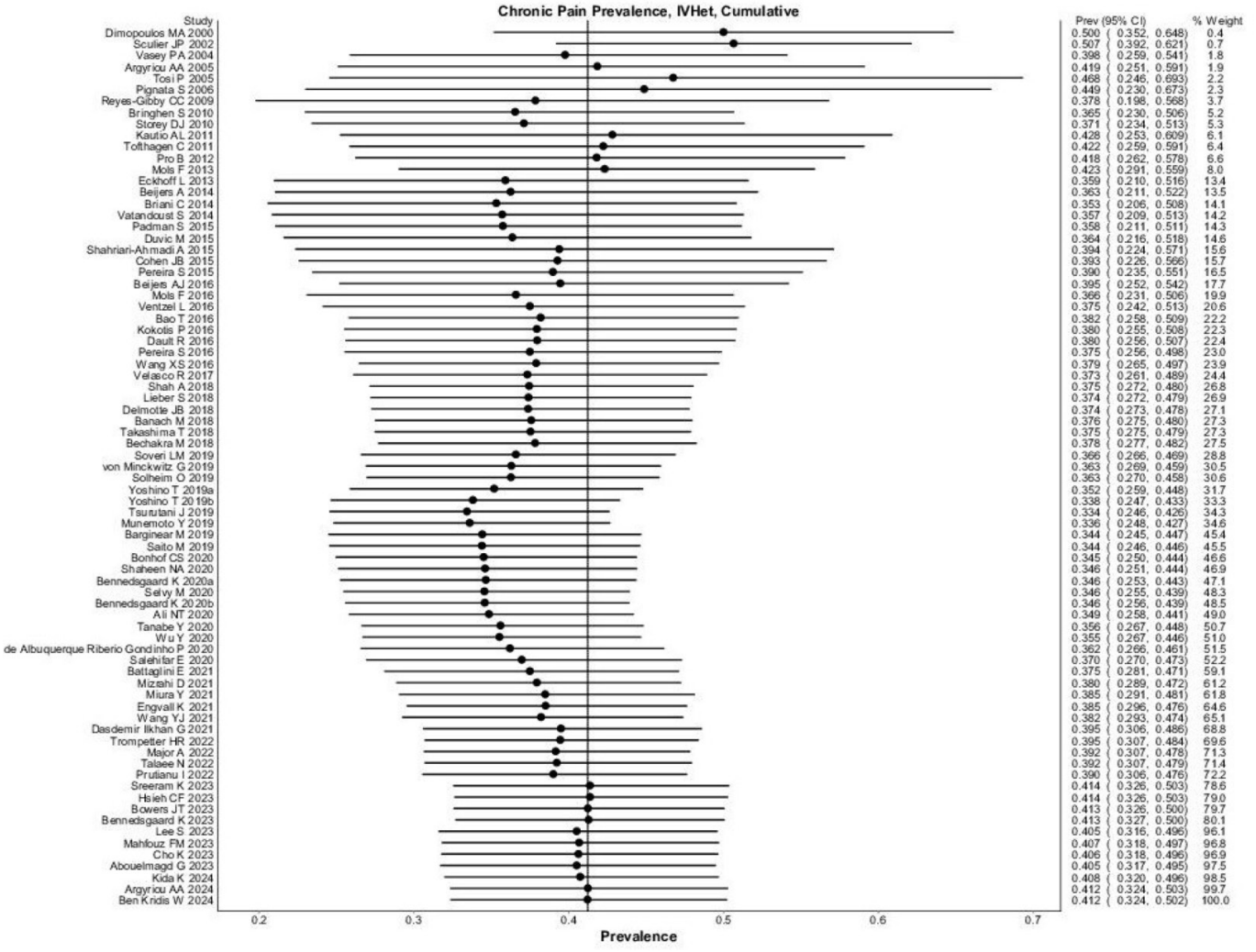

Figure 3 Cumulative meta-analysis forest plot of chronic painful chemotherapy induced peripheral neuropathy (CIPN). A cumulative meta-analysis, ordered by year, for point estimates is shown, using an inverse variance heterogeneity model. The black dots represent the pooled prevalence rate, while the left and right extremes of the dots represent the corresponding 95% CIs. The results of each corresponding study are pooled with all studies preceding it. IVHet, inverse variance heterogeneity model.

of chemotherapeutic agents with lower neurotoxicity, and the effectiveness of risk factor management and preventive care.

The elevated prevalence associated with both platinum-based agents and taxanes aligns with the existing literature that underscores their well documented neurotoxicity.[25] Sensory neurons in the dorsal root ganglia are highly susceptible to platinum-based chemotherapy-induced neurotoxicity, primarily due to DNA binding, which disrupts cellular function and can trigger apoptosis via abnormal cell cycle reactivation.[26] This leads to oxidative stress, mitochondrial dysfunction, and DNA damage, resulting in a distinctive, non-length dependent sensory neuronopathy.[26] Platinum-based agents can additionally bind to mitochondrial DNA, which contributes to prolonged neurotoxicity, including sensory symptoms with a length-dependent distribution.[26] The pathogenesis of CIPN induced by taxanes is thought to involve mechanisms such as ion channel disruption, mitochondrial dysfunction, impaired axonal transport, and inhibition of the neuroimmune response.[27] Furthermore, taxanes

Table 1 GRADE (Grading of Recommendations, Assessment, Development and Evaluation) evidence profile and summary of findings showing certainty in estimates for primary outcome

	GRADE domain					Summary of findings		Certainty in estimates
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Pooled prevalence (95% CI)	No of patients	
Prevalence of chronic painful CIPN	Minimal concerns related to non-response bias and ascertainment of outcome	Serious concerns (I^2=95%, heterogeneity in study design)	No serious concerns	Serious concerns (wide 95% CI and prediction interval)	Undetected	41.22% (32.40 to 50.19)	10962	Very low

CIPN, chemotherapy induced peripheral neuropathy.

tend to accumulate in the dorsal root ganglia, exacerbating damage to central sensory neurons.[28]

Prevalence rates also varied based on cancer types, with the highest being reported in those with lung cancer. This may be attributed to the complex nature of lung cancer treatment, particularly the frequent use of multiple and prolonged chemotherapy cycles.[29] Such treatments often result in higher cumulative exposure to neurotoxic agents. Specifically, non-small cell lung cancer is commonly treated with platinum-based chemotherapy regimens, such as cisplatin and carboplatin, which are well known for their high neurotoxicity profiles.[30] In contrast, lymphoma treatments may involve less neurotoxic regimens, such as anthracyclines or targeted therapies,[31 32] which may contribute to the lower prevalence of chronic painful CIPN.

Finally, prevalence rates of chronic painful CIPN have remained stable over time and despite the country's human development status, potentially reflecting stagnation in the advancement of treatment modalities for this pervasive and debilitating condition. This observation might also be attributed to the increasing use of more potent chemotherapeutic agents, which have higher neurotoxicity profiles. While opioid analgesics are fundamental in managing cancer pain, their role is less clear for patients in complete cancer remission who experience chronic pain. Concerns about opioid use in this group are heightened by the opioid epidemic, potential risks of substance use disorder, opioid-induced hyperalgesia, central sensitization, and other adverse effects.[33 34] Additionally, despite considerable progress in neuromodulation therapies over the past two decades,[8] no neuromodulation treatments have received approval from the US Food and Drug Administration for CIPN. Consequently, CIPN symptoms continue to present substantial treatment challenges, even with the advent of advanced therapeutic interventions.

Implications for research

The high prevalence and marked heterogeneity in prevalence estimates across regions suggest a need for large scale, multinational studies that capture diverse populations, particularly from under-represented regions, such as Africa, Asia, and South America. Addressing this gap could help provide a more accurate global estimate of chronic painful CIPN prevalence and elucidate regional factors, such as genetic susceptibility, healthcare quality, and chemotherapeutic practices, that may influence these outcomes. Additionally, the differential prevalence by cancer type and chemotherapy agent underscores the need for mechanistic studies that explore how various agents specifically affect sensory neurons and predispose patients to painful symptoms. Lastly, our findings highlight the stability of prevalence over time, suggesting that advancements in painful CIPN prevention and treatment remain limited. Future research should therefore prioritize innovative therapies and preventive strategies, including potential neuroprotective agents, to address this unmet need.

Strengths and potential limitations

To the best of our knowledge, this study represents the first meta-analysis to provide comprehensive global prevalence estimates for chronic painful CIPN among patients diagnosed with CIPN, thus addressing a significant gap in the existing literature. The analysis used an inverse variance heterogeneity model complemented by subgroup and meta-regression analyses to give robust insights. Additionally, the subgroup analysis sheds light on subpopulations with elevated prevalence rates, including specific chemotherapy regimens and primary cancer types. These findings are of considerable importance to clinicians, researchers, and public health authorities, especially oncologists, pain specialists, neurologists, and policy makers, in developing effective strategies to mitigate the global burden of chronic painful CIPN.

This study had several notable limitations. First, the statistical model did not account for individual study weights based on the population size of each country, which may lead to over-representation of data from countries with smaller populations and under-representation of those with larger populations. Second, substantial statistical heterogeneity was observed both in the primary outcome and in subgroup analyses, a common issue in prevalence meta-analyses that integrate diverse studies across global contexts. Third, the representation of certain subgroups was limited due to the small number of studies available, which may affect the reliability of the findings. According to the credibility criteria of Schandelmaier *et al*,[35] all subgroup analyses performed in the current study were considered 'very small' (1–2 studies in the smallest subgroup) or 'rather small' (3–4 studies in the smallest subgroup). Fourth, there may be variability in the diagnostic criteria for CIPN across studies, and the definition of chronic painful CIPN, particularly regarding severity thresholds for classifying chronic pain, may not have been uniformly applied. Fifth, the quality and design of the studies varied, which could introduce bias and affect the overall validity of the prevalence estimates. Sixth, there was a lack of data on long term outcomes and recovery rates for chronic painful CIPN, which limits the understanding of the condition's progression over time. Seventh, since this is an aggregate data meta-analysis, any subgroup and meta-regression results are considered exploratory and would need to be tested in original studies. Lastly, apart from the HDI metric, regional differences in healthcare systems and access to preventive measures and treatments were not accounted for, potentially influencing the prevalence rates reported.

CONCLUSION

In this meta-analysis, we highlighted the significant global burden of chronic painful CIPN, with >40% of patients diagnosed with CIPN having persistent painful neuropathy. However, the GRADE certainty of evidence was considered 'very low'. The wide variability in prevalence rates across different countries, continents, chemotherapy regimens, and primary cancer history underscores the need for tailored strategies to address this debilitating condition. Future studies should focus on elucidating the mechanisms underlying these disparities and developing interventions that can reduce the burden of chronic painful CIPN globally.

Contributors RSD: study conception, manuscript composition, data validation, data extraction and analysis, and supervision of all aspects of the study. CS: abstract screening, study selection, and data extraction. NH: study conception, data analysis and validation, editing, and supervision of study. SJ: data analysis and validation, editing, and supervision of study. LP: search strategy and composition of methods. YFH: abstract screening, study selection, and data extraction. RSD is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RSD received investigator initiated research grant funding from Nevro Corp and Saol Therapeutics paid to his institution.

Patient consent for publication Not applicable.

Ethics approval The study involved de-identified data from previously published studies and was therefore deemed exempt from institutional board review approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Ryan S D'Souza http://orcid.org/0000-0002-4601-9837
Nasir Hussain http://orcid.org/0000-0003-0353-1002
Saba Javed http://orcid.org/0000-0002-1028-8904

REFERENCES

1 Zhang X, Chen WW, Huang WJ. Chemotherapy-induced peripheral neuropathy. *Biomed Rep* 2017;6:267–71.
2 Song X, Wilson KL, Kagan J, *et al*. Cost of peripheral neuropathy in patients receiving treatment for multiple myeloma: a US administrative claims analysis. *Ther Adv Hematol* 2019;10:2040620719839025.
3 Hershman DL, Lacchetti C, Dworkin RH, *et al*. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *JCO* 2014;32:1941–67.
4 Starobova H, Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Front Mol Neurosci* 2017;10:174.
5 Loprinzi CL, Lacchetti C, Bleeker J, *et al*. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *JCO* 2020;38:3325–48.
6 D'Souza RS, Alvarez GAM, Dombovy-Johnson M, *et al*. Evidence-Based Treatment of Pain in Chemotherapy-Induced Peripheral Neuropathy. *Curr Pain Headache Rep* 2023;27:99–116.
7 D'Souza RS, Langford B, Wilson RE, *et al*. The state-of-the-art pharmacotherapeutic options for the treatment of chronic non-cancer pain. *Expert Opin Pharmacother* 2022;23:775–89.
8 D'Souza RS, Her YF, Jin MY, *et al*. Neuromodulation Therapy for Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review. *Biomedicines* 2022;10:1909.
9 Vu PD, McDonough KE, Dougherty PM, *et al*. Psychophysical and Functional Outcomes in Chemotherapy-induced Peripheral Neuropathy After Spinal Cord Stimulation: A Narrative Review and Case Series. *Neuromodulation: Technology at the Neural Interface* 2024;27:1305–20.
10 Seretny M, Currie GL, Sena ES, *et al*. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain* 2014;155:2461–70.
11 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
12 D'Souza RS, Barrington MJ, Sen A, *et al*. Systematic reviews and meta-analyses in regional anesthesia and pain medicine (Part II): guidelines for performing the systematic review. *Reg Anesth Pain Med* 2024;49:403–22.
13 Barrington MJ, D'Souza RS, Mascha EJ, *et al*. Systematic Reviews and Meta-analyses in Regional Anesthesia and Pain Medicine (Part I): Guidelines for Preparing the Review Protocol. *Reg Anesth Pain Med* 2023;doi.
14 Barrington MJ, D'Souza RS, Mascha EJ, *et al*. Systematic Reviews and Meta-analyses in Regional Anesthesia and Pain Medicine (Part I): Guidelines for Preparing the Review Protocol. *Anesth Analg Feb* 2024;138:379–94.
15 D'Souza RS, Barrington MJ, Sen A, *et al*. Systematic Reviews and Meta-analyses in Regional Anesthesia and Pain Medicine (Part II). *Anesth Analg* 2024;138:395–419.
16 Treede R-D, Rief W, Barke A, *et al*. A classification of chronic pain for ICD-11. *Pain* 2015;156:1003–7.
17 Dasic B, Devic Z, Denic N, *et al*. Human development index in a context of human development: Review on the western Balkans countries. *Brain Behav* 2020;10:e01755.
18 Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.
19 Doi SAR, Barendregt JJ, Khan S, *et al*. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. *Contemp Clin Trials* 2015;45:130–8.
20 Doi SAR, Furuya-Kanamori L, Thalib L, *et al*. Meta-analysis in evidence-based healthcare: a paradigm shift away from random effects is overdue. *Int J Evid Based Healthc* 2017;15:152–60.
21 Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc* 2018;16:195–203.
22 Murad MH, Sultan S, Haffar S, *et al*. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60–3.
23 Hunt C, Moman R, Peterson A, *et al*. Prevalence of chronic pain after spinal cord injury: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2021;46:328–36.
24 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
25 Weaver BA. How Taxol/paclitaxel kills cancer cells. *Mol Biol Cell* 2014;25:2677–81.
26 Staff NP, Cavaletti G, Islam B, *et al*. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. *J Peripher Nerv Syst* 2019;24 Suppl 2:S26–39.
27 Knoerl R, Mazzola E, Mitchell SA, *et al*. Measurement properties of brief neuropathy screening items in cancer patients receiving taxanes, platinums, or proteasome inhibitors. *J Patient Rep Outcomes* 2021;5:101.
28 Rattanakrong N, Siriphorn A, Boonyong S. Incidence density and factors associated with peripheral neuropathy among women with breast cancer during taxane-based chemotherapy. *Sci Rep* 2022;12:10632.
29 Vicidomini G. Current Challenges and Future Advances in Lung Cancer: Genetics, Instrumental Diagnosis and Treatment. *Cancers (Basel)* 2023;15:3710.
30 Miyawaki E, Kenmotsu H, Shintani Y, *et al*. Efficacy of platinum agents for stage III non-small-cell lung cancer following platinum-based chemoradiotherapy: a retrospective study. *BMC Cancer* 2022;22:342.
31 Hortobágyi GN. Anthracyclines in the treatment of cancer. An overview. *Drugs (Abingdon Engl)* 1997;54 Suppl 4:1–7.
32 Cai P, Hao J, Wang D, *et al*. Comparative efficacy of different chemotherapies for non-Hodgkin lymphoma: a network-meta analysis. *Oncotarget* 2017;8:91238–47.
33 Mudumbai SC, He H, Chen J-Q, *et al*. Opioid use in cancer patients compared with noncancer pain patients in a veteran population. *JNCI Cancer Spectr* 2024;8:pkae012.
34 D'Souza RS, Nahin RL. Nationally Representative Rates of Incident Prescription Opioid Use Among United States Adults and Selected Subpopulations: Longitudinal Cohort Study From the National Health Interview Survey, 2019 to 2020. *J Pain* 2024;25:104665.
35 Schandelmaier S, Briel M, Varadhan R, *et al*. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:E901–6.