Risk factors for oxaliplatin-induced peripheral neuropathy: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Oxaliplatin-induced neuropathy is a significant complication of cancer therapy. We aimed at investigating the risk factors of oxaliplatin-induced neuropathy (OIPN) and providing evidence to enhance its prevention.

MATERIALS AND METHODS: PubMed, Medline, Web of Science, Embase, China Knowledge Resource Integrated Database, and the Wanfang Database were searched comprehensively for observational studies investigating the prevalence and risk factors of OIPN from inception to November 30, 2021. The Newcastle-Ottawa Scale was used by two independent reviewers to assess methodological quality. When applicable, we used meta-analysis to determine mean differences and odds ratios for continuous and nominal scaled data.

RESULTS: We included 20 studies involving 10,900 participants for analysis. Factors associated with OIPN risk identified by meta-analysis were age, gender, diabetes, anemia, hypomagnesaemia, alcohol consumption, body mass index, body surface area, cumulative oxaliplatin dose and the number of chemotherapy cycles. Factors not associated with OIPN risk included smoking history and chemotherapy regimen.

CONCLUSIONS: This meta-analysis identified multiple variables associated with OIPN. The recognition of modifiable risk factors is an urgent priority to improve prevention and treatment outcomes.

Key Words: Oxaliplatin-induced peripheral neuropathy, Risk factor, Meta-analysis.

Introduction

Cancer is a major global public health problem. The International Agency for Research on Cancer estimated that 19.3 million incident cancer cases and 10 million cancer deaths occurred worldwide in 2020¹. Chemotherapy, as one of the primary methods of tumor treatment, can reduce the risk of recurrence and improve overall survival. However, complications of chemotherapy may degrade quality of life, and may require treatment modification or discontinuation. Oxaliplatin, a third-generation platinum-based anticancer agent, is effective against colorectal (CRC), ovarian, gastric, lung, and other cancers². The National Comprehensive Cancer Network recommends oxaliplatin-based combination chemotherapy as the first-line treatment for advanced CRC³. Through the combined use of leucovorin, 5-fluorouracil and other drugs, the efficacy rate of tumor treatment can reach 30-40%. Oxaliplatin-induced peripheral neuropathy (OIPN) is one of the major complications of this drug; over 70% of the patients receiving oxaliplatin are affected by some degree of sensory neuropathy, including ototoxicity and dysphonic syndrome⁴. An estimated 65-98% of oxaliplatin regimens experience an acute neuropathy that may begin within hours of infusion and may last up to 5-7 days⁵. Chronic sensory neuropathy may last up to 21 days or longer in patients receiving 12 cycles of chemotherapy⁶. Varying degrees of neuropathy develop in almost all patients treated with oxaliplatin⁷,⁸, and may persist in 84% after 2 years of follow-up⁹.

While chemotherapy can significantly reduce recurrence rates and improve 5-year survival, OIPN greatly degrades quality of life⁰,¹¹. Although duloxetine may relieve OIPN-induced pain, refractory or intolerable OIPN necessitate dose delays or reduction or drug cessation¹². Despite recent promising initiatives, there are still no
Risk factors for oxaliplatin-induced peripheral neuropathy

Oxaliplatin-induced peripheral neuropathy (OIPN) is a dose- and duration-dependent neuropathy associated with oxaliplatin treatment. The cumulative dose of oxaliplatin, duration of therapy, and combination with bevacizumab are significant risk factors. Other factors, such as age, female sex, body mass index (BMI), alcohol intake, and comorbidities like diabetes, may also contribute to the development of OIPN. The prevention and management of OIPN are crucial to improve patient outcomes.

Evaluation of Quality

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality and bias risk of case-control and cohort studies. The NOS has eight areas for methodological quality. Each study received an overall score of up to eight points. A score of 0-3 points was considered low quality, 4-6 points was considered moderate quality, and a score of 7-8 points was considered excellent quality. The methodological quality of randomized controlled trials (RCT) in this review was assessed using the Jadad scale. Baseline data, randomization, allocation concealment, blinding, patient withdrawal, and follow-up loss were documented and analyzed. Eligible studies were rated independently by two reviewers (RYW and XLL) who were blinded to the study authors and institutions, with disagreements settled at a consensus meeting.

Statistical Analysis

Data were processed and evaluated with the Cochrane Handbook software Review Manager, which is highly recommended (version 5.4). For dichotomous and continuous data, odds ratio (OR) and mean difference (MD) were utilized, respectively, with 95% confidence intervals (CIs). Forest charts were utilized for the heterogeneity test, sensitivity analysis, and bias report.

In accordance with the Cochrane Handbook, various effect models and heterogeneity analyses were performed. The retrieved data were merged and compared using a fixed-effect model if the included studies reported the same risk factor. If the fixed-effect model revealed heterogeneity analysis ($I^2 > 50\%$), a random-effect model and sensitivity analysis would be utilized. When the MD data was equivalent to the OR data, we applied a random-effects model. Statistical significance was determined by a $p$-value lower than 0.05.

This study was performed based on the PRISMA checklist.
Results

Literature Search Results

Our review of the literature yielded 4,337 clinical trials. A total of 2,357 trials were initially excluded after removing duplicated publications and reviewing titles and abstracts. We then excluded 35 trials after reviewing the full texts of the remaining 55 studies. The reasons for their exclusion are listed in Figure 1. Finally, 20 studies were chosen for meta-analysis. Figure 1 summarizes the study screening and selection process.

Characteristics and Quality of Included Clinical Trials

We included 20 studies involving 10,900 participants for analysis, including 11 cohort studies, 7 case-control studies, and 2 RCT (Table I). The methodological quality evaluation scores of the 20 studies were all above 5, indicating that the quality of the included studies was high (Tables II-IV).

Age

Twelve studies evaluated age as a risk factor for OIPN. Means and SDs were extracted from 8 studies, while raw counts were extracted from 4 studies of OIPN and non-OIPN participants. We performed a subgroup analysis of OIPN severity based on the NCI-CTCAE scale. As the forest plot indicates, there was no difference between patients ≤ 60 years of age and those older than 60 years (p=0.30, OR=1.13, 95% CI=0.90-1.41; Figure 2A). However, the incidence of OIPN increased significantly with age (CRC patients: p<0.0001, MD=1.76, 95% CI=0.92-2.60; other cancer patients: p<0.00001, MD=7.92, 95% CI=5.86-9.98; Figure 2B).

Gender

Ten studies investigated gender as a risk factor for OIPN. According to the severity of OIPN, we performed different subgroup analysis based on the NCI-CTCAE scale. The meta-analysis showed that females were at greater risk for severe OIPN (p=0.003, OR=1.34, 95% CI=1.11-1.63, Figure 3), and also identified a significant relationship between female sex and severe OIPN based on pooled OR (p=0.01, OR=1.97, 95% CI=1.16-3.34).

Diabetes

Eight studies evaluated diabetes as a risk factor for OIPN. The meta-analysis disclosed a significantly different incidence of OIPN between diabetic and non-diabetic patients (p=0.01, OR=0.70, 95% CI=0.53-0.92; Figure 4).

Figure 1. Study inclusion and exclusion flow diagram.
### Table 1. Summary of characteristics.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type of study</th>
<th>Type of cancer</th>
<th>Sample size</th>
<th>Chemotherapy regimens</th>
<th>Scale</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argyriou et al.</td>
<td>2012</td>
<td>Spain</td>
<td>Prospective cohort</td>
<td>Colorectal</td>
<td>150</td>
<td>1. FOLFOX-4; 2. XELOX</td>
<td>NCI-CTCAE v.3</td>
<td>Chemotherapy regimen</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>2012</td>
<td>USA</td>
<td>Retrospective case-control</td>
<td>Colorectal</td>
<td>60</td>
<td>Oxaliplatin</td>
<td>NCI-CTC</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Cho et al.</td>
<td>2012</td>
<td>Japan</td>
<td>Retrospective case-control</td>
<td>Advanced gastric</td>
<td>85</td>
<td>Mfolfox 6</td>
<td>NCI-CTCAE v.3</td>
<td>Age</td>
</tr>
<tr>
<td>Vincenzi et al.</td>
<td>2013</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>169</td>
<td>FOLFOX IV</td>
<td>NCI-CTCAE v.3</td>
<td>Albuminemia, hypomagnesemia, alcohol consumption</td>
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<tr>
<td>Alejandro et al.</td>
<td>2013</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>422</td>
<td>FOLFOX-6</td>
<td>NCI-CTCAE v.3</td>
<td>Gender, age, BMI, BSA, OXA cumulative dose, diabetes</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2013</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>171</td>
<td>FOLFOX-4</td>
<td>NCI WHO</td>
<td>Anemia, Hypomagnesemia, alcohol consumption, chemotherapy cycles</td>
</tr>
<tr>
<td>Velasco et al.</td>
<td>2014</td>
<td>Spain, Greece, Italy</td>
<td>Prospective cohort</td>
<td>Colorectal</td>
<td>200</td>
<td>1. FOLFOX-4; 2. Mfolfox-6; 3. XELOX</td>
<td>Tnsc, NCI-CTC v.3</td>
<td>Gender, OXA cumulative dose</td>
</tr>
<tr>
<td>Beijers et al.</td>
<td>2015</td>
<td>Netherlands</td>
<td>Prospective cohort</td>
<td>Colorectal</td>
<td>207</td>
<td>1. FOLFOX; 2. CAPOX</td>
<td>EORTC QLQ-CIPN20</td>
<td>OXA cumulative dose</td>
</tr>
<tr>
<td>Shahriari-Ahmadi et al</td>
<td>2015</td>
<td>Tehran</td>
<td>Retrospective case-control</td>
<td>Colorectal</td>
<td>130</td>
<td>1. FOLFOX; 2. XELOX</td>
<td>NCI-CTC v.3</td>
<td>BMI, anemia, Hypomagnesemia</td>
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<tr>
<td>Ottiano et al.</td>
<td>2016</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>102</td>
<td>CAPOX</td>
<td>NCI-CTCAE v.4</td>
<td>Diabetes, BMI (G2-G3)</td>
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<td>Tanishima et al.</td>
<td>2017</td>
<td>Japan</td>
<td>Retrospective case-control</td>
<td>Colorectal</td>
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<td>1. FOLFOX-6; 2. CAPOX</td>
<td>NCI-CTCAE v.4</td>
<td>Gender, OXA cumulative dose</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2017</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>225</td>
<td>Oxaliplatin</td>
<td>NCI-CTC</td>
<td>Age, diabetes, OXA cumulative dose</td>
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<tr>
<td>Gaballah et al.</td>
<td>2018</td>
<td>Egypt</td>
<td>Retrospective case-control</td>
<td>Colorectal</td>
<td>250</td>
<td>1. Paclitaxel; 2. Docetaxel; 3. Cisplatin; 4. Oxaliplatin</td>
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<td>Diabetes, OXA cumulative dose</td>
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<tr>
<td>Iveson et al.</td>
<td>2018</td>
<td>England</td>
<td>RCT</td>
<td>Colorectal</td>
<td>6,088</td>
<td>1. FOLFOX; 2. CAPOX</td>
<td>NCI-CTC v.3</td>
<td>Duration (3 m vs. 6 m)</td>
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<tr>
<td>Zhang</td>
<td>2018</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>242</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE v.4</td>
<td>Antibiotic, OXA cumulative dose</td>
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<tr>
<td>Yildirim et al.</td>
<td>2020</td>
<td>Japan</td>
<td>Retrospective cohort</td>
<td>Colorectal</td>
<td>186</td>
<td>1. FOLFOX; 2. XELOX</td>
<td>NCI-CTCAE v.3</td>
<td>Age, gender, height, BSA, hemoglobin, Vd, glucose, magnesium</td>
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<tr>
<td>Sheng</td>
<td>2019</td>
<td>China</td>
<td>Retrospective case-control</td>
<td>Colorectal</td>
<td>268</td>
<td>XELOX</td>
<td>NCI-CTCAE v.4</td>
<td>Diabetes, alcohol consumption, OXA cumulative dose, ALT</td>
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<td>Yoshino et al.</td>
<td>2019</td>
<td>Japan</td>
<td>RCT</td>
<td>Colon</td>
<td>1313</td>
<td>1. FOLFOX-6; 2. CAPOX</td>
<td>NCI-CTCAE v.4</td>
<td>Duration (3 m vs. 6 m)</td>
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<td>Mizrahi et al.</td>
<td>2021</td>
<td>Australia</td>
<td>Retrospective case-control</td>
<td>Colorectal, breast, ovarian</td>
<td>330</td>
<td>Oxaliplatin</td>
<td>NCI-CTCAE v.4, Tnsc</td>
<td>Age, gender, BSA</td>
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</tbody>
</table>

Cohort was truly or somewhat representative of a typical OIPN cohort
OIPN and on-OIPN cohorts were from the same community
Ascertainment of OIPN was made via secure record OR structured interview
Demonstration that outcome of interest was not present at start of study
Cohorts were comparable on the basis of the design OR confounders controlled for
Assessment of outcome was independent OR linked to medical records
Follow-up was long enough for outcomes to occur
Adequate follow up of cohorts

<table>
<thead>
<tr>
<th>Table II. Quality assessment for cohort studies.</th>
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<td>Cohort was truly or somewhat representative of a typical OIPN cohort</td>
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4032
Adequate definition with independent validation
Consecutive or obviously representative series of cases
Selection of community controls
No history of disease (endpoint) in controls
Comparability of cases and controls based on design or analysis
Assessment of outcome from secure record OR structured interview
Same method of ascertainment for cases and controls
Same response rate for both groups

<table>
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<th>Study</th>
<th>Adequate definition with independent validation</th>
<th>Consecutive or obviously representative series of cases</th>
<th>Selection of community controls</th>
<th>No history of disease (endpoint) in controls</th>
<th>Comparability of cases and controls based on design or analysis</th>
<th>Assessment of outcome from secure record OR structured interview</th>
<th>Same method of ascertainment for cases and controls</th>
<th>Same response rate for both groups</th>
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<td>Cho et al18 2012</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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### Table IV. Quality assessment of RCTs.

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<th>Study ID</th>
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<th>Allocation Concealment</th>
<th>Inclusion Criteria</th>
<th>Blinding</th>
<th>Drop-off (%)</th>
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<td>Iveson et al2018</td>
<td>Minimization algorithm incorporating a random component</td>
<td>Open label</td>
<td>Comparable ((p&lt;0.05))</td>
<td>Non-blinded</td>
<td>0.3</td>
</tr>
<tr>
<td>Yoshino et al34 2019</td>
<td>Dynamic allocation</td>
<td>Open label</td>
<td>Comparable ((p&gt;0.05))</td>
<td>Non-blinded</td>
<td>1.6</td>
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</tbody>
</table>

**Figure 2.** Meta-analysis of age.
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Anaemia

Four studies\(^{19,21,24,32}\) explored the role of anaemia as a risk factor for OIPN. The meta-analysis results showed a significant different incidence of OIPN between anaemic and non-anaemic patients (\(p=0.0007, \text{OR}=0.39, 95\% \text{ CI}=0.22-0.67\); Figure 5).

Hypomagnesaemia

Three studies\(^{19,21,24}\) assessed the role of hypomagnesaemia as a risk factor for OIPN. The meta-analysis indicated that there was significantly increased incidence of OIPN in hypomagnesaemic compared with non-hypomagnesaemic patients (\(p<0.00001, \text{OR}=0.30, 95\% \text{ CI}=0.20-0.46\); Figure 6).

Alcohol Consumption

Four studies\(^{19,21,27,33}\) examined alcohol consumption as a risk factor for OIPN. One\(^{27}\) of the studies

Figure 3. Meta-analysis of gender.

Figure 4. Meta-analysis of diabetes.
used a different evaluation standard from the other three, so we finally combined the three articles for analysis. The meta-analysis showed that alcohol consumption was a risk factor for OIPN ($p=0.001$, OR=0.42, 95% CI=0.25-0.70; Figure 7).

**Smoking History**

Five studies evaluated smoking history as a risk factor for OIPN. The meta-analysis showed no difference in the incidence of OIPN between patients with and without smoking histories ($p=0.51$, OR=1.13, 95% CI=0.79-1.62; Figure 8).

**Body Mass Index**

Five studies provided strong evidence from that increased BMI was a risk factor for OIPN. Three studies indicated that the incidence of OIPN was higher when BMI was > 25 ($p<0.00001$, OR=0.21, 95% CI=0.14-0.32; Figure 9A). Two studies showed that patients with higher BMIs carried a greater risk of peripheral neuropathy as a complication of chemotherapy ($p=0.02$, MD=2.03, 95% CI=0.26-3.79; Figure 9B).

**Body Surface Area (BSA)**

Three studies investigated the role of BSA as a risk factor for OIPN. The results of one study was recorded differently from those of other reports and could not be analyzed together, so we finally combined the two articles for analysis. The meta-analysis showed that the risk of OIPN was directly related to body surface area ($p<0.00001$, MD=0.09, 95% CI=0.05-0.12; Figure 10).

**Chemotherapy Regimens**

Six studies evaluated chemotherapy regimens as risk factors for OIPN. One report did not provide precise data, thus we included 5 studies for evaluation. The meta-analysis provided low evidence that chemotherapy regimens were OIPN risk factors ($p=0.86$, OR=1.10, 95% CI=0.94-1.28; Figure 11).

**Cumulative Oxaliplatin Dose**

Six studies gave strong evidence that the cumulative dose of oxaliplatin was a risk factor for OIPN. Three studies showed that the cumula-
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Dose of oxaliplatin and the risk of OIPN were directly related ($p<0.00001$, MD=127.24, 95% CI=101.90-152.58; Figure 12A). Furthermore, three other studies showed that the incidence of OIPN was significantly higher in patients receiving a cumulative dose of oxaliplatin > 500 mg than in those who had received < 500 mg ($p<0.00001$, OR=0.37, 95% CI=0.27-0.50; Figure 12B).

Chemotherapy Cycles
Six studies investigated the number of chemotherapy cycles as a risk factor for OIPN. Two studies used different evaluation standards than the other reports, so we consequently combined four articles for analysis. The meta-analysis showed that patients receiving more than six cycles were more likely to develop OIPN ($p<0.00001$, OR=0.26, 95% CI=0.20-0.34; Figure 13).

Discussion
Our meta-analysis of 20 studies found statistically significant associations between OIPN and ten factors: age, gender, diabetes, anemia, hypomagnesaemia, alcohol consumption, BMI, BSA, cumulative oxaliplatin dose, and the number of chemotherapy cycles.

The pooled prevalence of OIPN was higher in older than in younger patients. Because of age-related physiologic decline, the treatment of elderly cancer patients is more likely to induce side effects. Peripheral nerve function and synaptic density decrease with age. Therefore, elderly chemotherapy recipients are more vulnerable to the development of peripheral neuropathy. Additionally, although the incidence of OIPN will increase with age, it is not based on the age of 60 years.

Ovarian estrogen production decreases rapidly before and after menopause. Estrogen has a protective effect on peripheral nerves and an antioxidant stress function that can play a neuroprotective role by improving mitochondrial function. Our study identified female sex as having a predisposition to OIPN and severe OIPN based on meta-analysis results. Since all participants were older than 60 years of age, and because most women experience menopause between the...
ages of 45 and 54 years, they were more prone to OIPN, and especially to severe OIPN.

Comorbidities are also risk factors of OIPN. Our results suggest that patient with diabetes, anaemia, and hypomagnesaemia are at increased risk of OIPN. Diabetes injures peripheral nerve tissue by inducing oxidative stress, inflammation, and abnormal lipid metabolism, and by reducing the levels of neuroprotective factors. Oxidative stress is a pathogenic mechanism shared by diabetic neuropathy and OIPN. Diabetes can not only exacerbate OIPN through oxidative stress, but also through several other pathways. A mechanism distinct from oxaliplatin-induced neuropathy injures peripheral nerves concurrently, thereby increasing the incidence of OIPN.

Anaemia decreases blood oxygen carrying capacity and impairs aerobic metabolism in multiple organs. Hypoxia of the nervous system reduces the activation of cerebral neurons and inhibits nerve conduction. Additionally, iron deficiency may inhibit myelin production, impair synaptogenesis, and compromise basal ganglia function, adversely affecting psychomotor development and intellectual ability.

Calcium ion influx initiates a series of cytotoxic cascade reactions that may end in neuronal apoptosis. Magnesium ion is a calcium ion channel blocker and N-methyl-D-aspartate receptor antagonist that can reduce calcium influx and participate in a series of metabolic processes, thereby conferring neuroprotection. Thus, calcium and magnesium infusions have been used to prevent or minimize the neuropathy associated with oxaliplatin therapy.

Chronic alcohol consumption will lead to alcoholic peripheral neuropathy characterized by sensory impairment. Alcohol-induced neuropathogenesis is complex, and may result from the direct neurotoxicity of alcohol combined with
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Nutritional deficiencies that complicate long-term drinking. Studies of the correlation between drinking history and neuropathy have shown that peripheral nerve injury is positively correlated with the total capacity for alcohol and drinking time, which prove the direct toxicity of alcohol on peripheral nerve. Consequently, patients with a history of alcohol consumption may have pre-existing peripheral nerve damage, which is manifested by a predisposition to OIPN.

Oxaliplatin/leucovorin/5-fluorouracil combination therapy is a first-line treatment in clinical oncology and offers significant benefits for patients with advanced CRC. A previous study evaluated oxaliplatin-induced peripheral neuropathy in CRC patients treated with folinic acid, fluorouracil and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (XELOX). While the incidence rates of acute neurotoxicity during FOLFOX and XELOX therapies were comparable, FOLFOX was associated with a higher incidence of chronic neuropathy. However, our results indicate that chemotherapy regimen was not a risk factor for OIPN.

Oxaliplatin can injure nerve tissue by accumulating in dorsal root ganglia and causing oxidative stress and ion channel dysfunctions. When the accumulation of oxaliplatin in dorsal root ganglia neurons is greater than its elimination, tissue drug levels rise and increase the risk of neurotoxicity. The cumulative dose of oxaliplatin is a well-known risk factor for oxaliplatin-induced chronic neuropathy. An international multicenter study found that when the median cumulative dose of

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**Figure 11.** Meta-analysis of chemotherapy regimens.

**Figure 12.** Meta-analysis of chemotherapy regimens.
oxaliplatin was 810 mg/m², 24.1% of patients had persistent neuropathic symptoms. Park et al demonstrated that in a patient population with a mean cumulative dose of oxaliplatin of 766 mg/m², 92% experienced acute neuropathy, with 16% eventually developing severe neuropathy > grade 3. However, another study concluded that OIPN was unrelated to dose. Our meta-analysis shows that high doses are associated with OIPN, especially when the cumulative dose exceeds 500 mg, a smaller dose than reported in previous studies. In a future study, we could explore the maximum tolerated cumulative dose without incurring potentially irreversible nerve damage in such high-risk patients to inform effective patient screening.

Based on the results of this study, we found that OIPN is related to many factors. Clinically, we need to identify these risk factors early and take corresponding methods to prevent OIPN or reduce its impact on patients. The results of this study suggest that in the clinical application of oxaliplatin-based regimen for tumor patients with other diseases (such as diabetes, anaemia, hypomagnesaemia), we should pay more attention to the occurrence of peripheral neuropathy and take active preventive measures. Moreover, tumor patients should maintain good living habits during oxaliplatin chemotherapy, avoid drinking alcohol and pay attention to weight management. If clinical patients need to use oxaliplatin chemotherapy continuously, especially when the cumulative dose above 500 mg/m², special attention should be paid to the prevention of neuropathy. It is reasonable to adjust or discontinue oxaliplatin and switch to an oxaliplatin-free chemotherapy regimen when significant neuropathy develops during treatment. In addition, a comprehensive panel of 8 polymorphisms has been validated as significant markers related to oxaliplatin toxicity. Genetic variants and predictive markers may allow physicians to improve the efficacy of cancer therapy.

This review has several limitations. Firstly, the patient inclusion and exclusion criteria, sample sizes, the age distributions and gender ratios, the prevalence rates of comorbidities, and the assessment tools. Moreover, the observation frequencies and times of the analyzed reports were significantly different, resulting in scattered and relatively heterogeneous results of all included investigations. Secondly, there were multiple and varied influencing factors reported in the included literature. Some factors were addressed by only a few articles and could not be subjected to meta-analysis, needing to be evaluated only by descriptive analysis.

Conclusions

This meta-analysis identified multiple variables associated with OIPN. The recognition of modifiable risk factors is an urgent priority to improve prevention and treatment outcomes.

Availability of Data and Materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Authors’ Contributions
XHD contributed conception and design of the study. RYW and QHS organized the databases. RYW, XLL, QHS, and...
STX performed the statistical analysis and prepared the figures and tables. XHD, RYW, and XLL wrote the first draft of the manuscript. STX and QHS wrote the sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of Interest
All authors have no conflict of interests in this study.

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References
20) Alejandro L, Behrendt CE, Chen K, Openshaw H, Shibata S. Predicting acute and persistent neurop-
22) Velasco R, Bruna J, Briani C, Argyriou AA, Kalo-
fonos HP. Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer pa-
23) Beijers AJ, Mols F, Tjan-Heijnen VC, Faber CG, van de Poll-Fransen LV, Vreugdenhil G. Peripheral neuropathy in colorectal cancer survivors: the in-
24) Shahriari-Ahmadi A, Fahimi A, Payandeh M, Sa-
27) Wang Y, Yang X, Wei X. Analysis of factors affect-
28) Gaballah A, Shafik A, Elhusseiny K, Mai A. Che-
29) Molassiotis A, Cheng HL, Leung KT, Li YC, Lopez V, Risk Risk factors for chemotherapy-induced pe-
30) Iveson TJ, Kerr RS, Saunders MP, Cassidy J, Hol-
31) Zhang MY. Analysis of the relationship between antibiotics exposure and oxaliplatin-induced neu-
32) Yildirim N, Cengiz M. Predictive clinical factors of chronic peripheral neuropathy induced by oxal-
33) Sheng FR. Study on the relationship between the risk of chemotherapy-induced peripheral neuropa-
34) Yoshino T, Yamanaka T, Oki E, Kotaka M, Manaka D, Eto T, Hasegawa J, Takagane A, Nakamura M, Kato T, Munemoto Y, Takeuchi S, Bando H, Tan-
guchi H, Gamoh M, Shiozawa M, Mizushima T, Saji S, Maehara Y, Ohtsu A, Mori M. Efficacy and long-term peripheral sensory neuropathy of 3 Vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the achieve phase 3 random-
ized clinical trial. JAMA Oncol 2019; 5: 1574-1581.
stein D. Hemoglobin, body mass index, and age as risk factors for paclitaxel- and oxaliplatin-in-
duced peripheral neuropathy. JAMA Netw Open 2021; 4: e2036695.
37) Verdú E, Ceballos D, Vilches JJ, Navarro X. In-
39) Jia G, Aroor AR, Sowers JR. Estrogen and mitochon-
drial function in cardiorenal metabolic syndrome. Prog Mol Biol Transl Sci 2014; 127C: 229-249.
40) Broffain E, Gruenbaum SE, Boyko M, Kutz R, Zlo-
653.
41) Sifuentes-Franco S, Pacheco-Moisés FP, Rodrí-
42) Malacrida A, Meregalli C, Rodriguez-Menendez V, Nicolini G. Chemotherapy-induced peripheral neu-


