

# Exploring the experiences of distal-extremity cryotherapy in preventing Chemotherapy-Induced Peripheral Neuropathy (CIPN) with Paclitaxel administration in people affected by breast cancer – A systematic review

Kelly Ford <sup>a,b,d</sup>, Maree Duddle <sup>a,b</sup>, Murray Turner, Catherine Paterson <sup>a,b,c</sup> – <sup>a</sup> Faculty of Health, University of Canberra, Bruce ACT, Australia; <sup>b</sup> Caring Futures Institute, Flinders University, Adelaide; <sup>c</sup> Central Adelaide Local Health Network; <sup>d</sup> ACT Health

## Background

### Global burden:

- 2.3 million new breast cancer cases and 685,000 deaths were reported in 2020.[1]

### Paclitaxel chemotherapy:

- Standard treatment for breast cancer, however, can cause significant toxicities, including chemotherapy-induced peripheral neuropathy (CIPN).[2]

### Impact of CIPN:

- CIPN affects sensation and causes pain in the hands and feet, directly influencing mortality outcomes due to treatment delays, dose reductions, and discontinuation.[3-5] Symptoms range from temporary changes in sensation to chronic pain, affecting daily life and quality of life.[3-5]

### Prevalence:

- Approximately 80% of patients experience CIPN, with 25% needing dose reductions and 41% facing long-term side effects.[6,7]

## Aim

To explore the experiences of utilising distal-extremity cryotherapy in reducing CIPN during Paclitaxel treatment on physical functioning, clinical outcomes, patient-reported outcomes, and healthcare service usage compared to standard care in people affected by breast cancer.

## Methods

CINAHL, Cochrane Library, Scopus, and Web of Science Core Collection databases were searched for English-language studies exploring the experiences of breast cancer patients treated with Paclitaxel utilising distal-extremity cryotherapy in reducing CIPN.

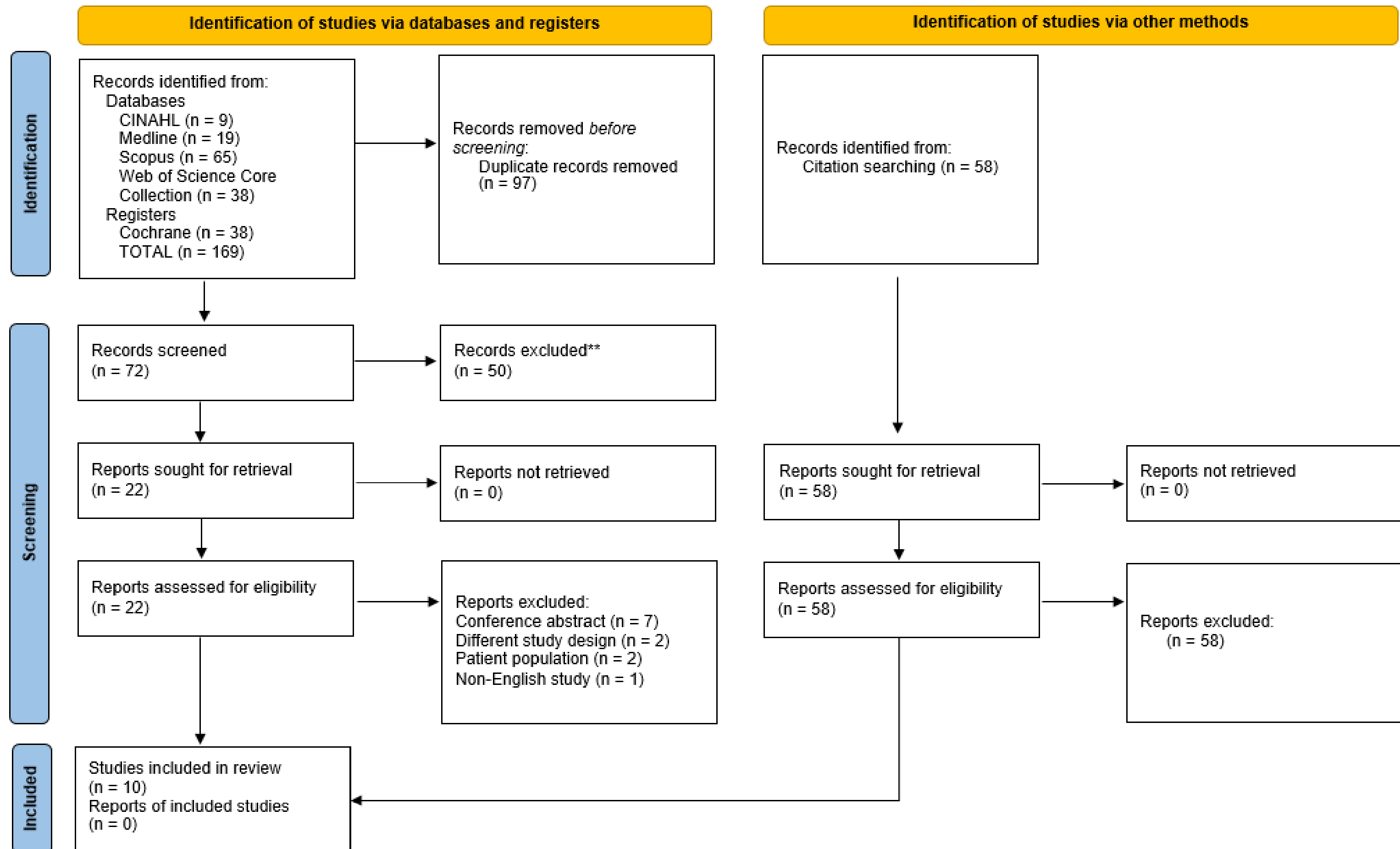


Figure 1: PRISMA Flowchart

## Results

- 130 publications were screened, and ten studies were included in this review (Figure 1). Across the ten studies, 561 participants were included, with 500 participants represented in the analysis.
- Three modes of cryotherapy were identified in the included ten studies (Table 1), crushed ice (One study), frozen gel cryotherapy (Eight studies), and continuous flow hypothermia (Two studies).
- Physical functioning and clinical outcomes:**
  - Mixed results; some studies reported modest improvements in CIPN symptoms.
  - Risk of bias and placebo effect due to blinding challenges.
  - Need for better-designed, larger-scale trials.
- Pain assessments:**
  - Continuous flow hypothermia appears promising in reducing pain.
  - Standardized pain assessment tools are required for future trials.
- Cryotherapy tolerance:**
  - Primary reason for participant attrition.
  - No serious adverse events or frostbite reported. Adverse events: numbness, tingling, redness, skin irritation.
- Patient-Reported Outcome Measures (PROMs):**
  - Greater improvements in the intervention group using cryotherapy.
  - Reduction in prevalence and severity of CIPN symptoms.
- Quality of life:**
  - Inconclusive impact on quality of life.
  - Need for comprehensive, longitudinal assessment tools in future studies.
- Healthcare service usage:**
  - Not reported.

Author/year/ country	Intervention	Application	Cryotherapy storage range (°C)
Coolbrandt et al. (2022) Belgium	<b>Frozen gel cryotherapy:</b> Gloves and socks (Study used gloves as both gloves and as socks). L) hand + foot. <b>Continuous flow hypothermia:</b> R) arm + leg.	<b>Frozen gel cryotherapy:</b> Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 45 minutes. <b>Continuous flow hypothermia:</b> Applied 30 minutes prior, during (60 minutes) and 30 minutes post.	<b>Frozen gel cryotherapy:</b> Stored at -18°C to -20°C. <b>Continuous flow hypothermia:</b> Constant temperature of 10°C-12°C.
Griffiths et al. (2018) United States of America	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hand + Foot: One sided (Dominant or non-dominant).</li></ul>	Applied for 210 minutes for Paclitaxel therapy each time. 15 minutes prior, during (180 minutes) and 15 minutes post. Changing gloves and socks every 45-50 minutes.	Stored at -25 to -30°C
Hanai et al. (2018) Japan	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hand + Foot: One sided (Dominant side).</li></ul>	Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 45 minutes.	Not reported.
Jue et al. (2022) United States of America	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hands + Feet: Both L) + R).</li></ul>	Applied for 75 minutes for Paclitaxel therapy each time. 15 minutes prior and during (60 minutes). Changing gloves and socks every 45 minutes.	Stored at -20°C to -24°C.
Ng et al. (2020) Singapore	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hands + Feet: Both L) + R).</li></ul>	Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 30 (+5) minutes.	Stored at -20°C (Gloves) and -10°C (Socks).
Rosenbaek et al. (2020) Denmark	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hands + feet: Both L) + R).</li></ul>	Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 45 minutes.	Stored at approx. -20°C for 3 hours prior to use.
Ruddy et al. (2019) United States of America	<ul style="list-style-type: none"><li>Crushed ice cryotherapy.</li><li>Hands and feet L) + R).</li></ul>	Patient hands covered with cotton gloves, quart-sized plastic bags 2/3 filled with ice applied on palm and dorsum of hands. Feet covered with cotton socks and similar 1/2 gallon sized bags filled with crushed ice applied to soles and roof of feet. Applied 15 minutes before and remained 15 minutes post treatment. Ice changed at request of patient.	Not reported.
Shigematsu et al. (2020) Japan	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves and socks.</li><li>Hands + Feet: Both L) + R).</li></ul>	Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 45 minutes.	Stored at -20°C.
Sundar et al. (2017) Singapore	<ul style="list-style-type: none"><li>Continuous flow hypothermia.</li><li>Arm and leg: One sided (Side of body randomised).</li></ul>	Applied for a total of 150 minutes. 60 minutes prior, during (60 minutes) and 30 minutes post.	Constant temperature of 22°C.
Yang et al. (2022) Taiwan	<ul style="list-style-type: none"><li>Frozen gel cryotherapy: Gloves.</li><li>Hand: One sided (Dominant side).</li></ul>	Applied for 90 minutes for Paclitaxel therapy each time. 15 minutes prior, during (60 minutes) and 15 minutes post. Changing gloves and socks every 45 minutes.	Stored at -24.3°C to -24.7°C

Table 1: Overview of distal-extremity cryotherapy interventions

## Limitations

The inherent heterogeneity in assessment tools and study designs among the included studies posed significant challenges for effectively conducting direct comparisons (Figure 2). This diversity makes it challenging to draw overarching conclusions and highlights the need for core outcome sets in future research.

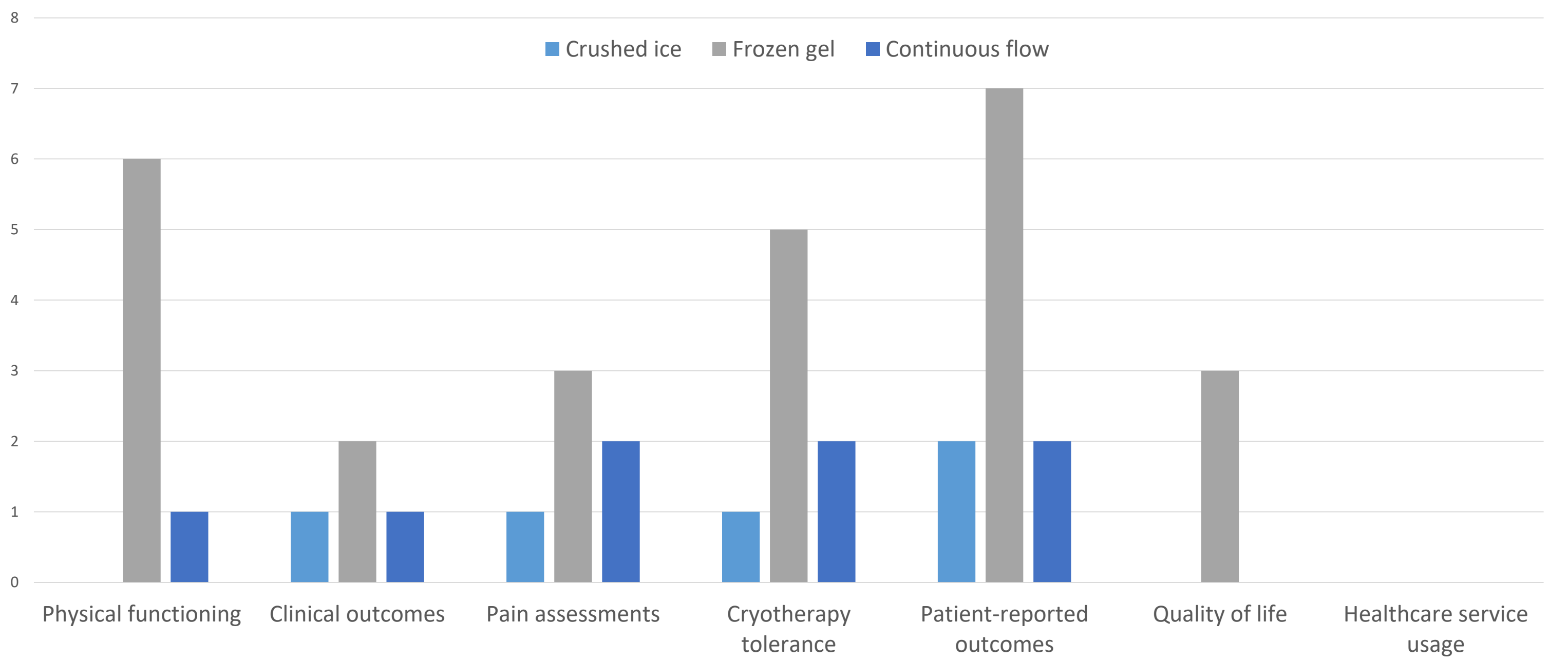


Figure 2: Heterogeneity of outcome measures by mode of cryotherapy - Total number of different outcome measures utilised for each mode of cryotherapy within the included studies.

## Conclusion

Distal-extremity cryotherapy is a safe intervention with minimal risk for serious adverse events. However, insufficient data supports the mainstay clinical use of cryotherapy in reducing CIPN from Paclitaxel use within the breast cancer population. Small sample sizes alongside heterogeneity in study design, cryotherapy mode, and measurement tools underscore the need for additional research.

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