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SMARTPHONE-BASED OBJECTIVE OUTCOME MEASURES IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW OF VALIDITY AND CLINICAL UTILITY

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating sequela of cancer treatment, traditionally assessed through subjective patient-reported outcomes (PROs) and clinical examinations. These methods are susceptible to bias and may lack sensitivity. Smartphone sensor technology offers a promising alternative for objective, quantifiable, and accessible monitoring of CIPN symptoms, particularly balance and autonomic dysfunction.

Objective: This systematic review aimed to critically evaluate the validity, reliability, and clinical utility of smartphone-based objective outcome measures for assessing balance and autonomic function in patients with CIPN.

Methods: A systematic search was conducted in PubMed, Scopus, CINAHL, IEEE Xplore, and Cochrane Library databases from inception to December 2018. Studies were included if they evaluated the use of smartphone sensors (accelerometers, gyroscopes, cameras) to assess balance, gait, or heart rate variability (HRV) in adults with CIPN or related peripheral neuropathies. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Results: Out of 327 records identified, five studies met the inclusion criteria. No studies were found that validated smartphone sensors exclusively in a CIPN population; thus, studies in diabetic peripheral neuropathy (DPN) and other neuropathies were included. The reviewed studies demonstrated strong concurrent validity of smartphone accelerometry for measuring postural sway against laboratory-grade force plates (correlation coefficients r = 0.82–0.94). Smartphone photoplethysmography (PPG) for HRV assessment showed excellent agreement with electrocardiography (ECG) for time-domain parameters (RMSSD ICC > 0.85) in controlled, resting conditions. Evidence for reliability and validity in home-based settings was limited.

Conclusion: Pre-2018 evidence, primarily from non-CIPN neuropathies, strongly supports the criterion validity of smartphone-based accelerometry for balance assessment and PPG for HRV measurement in controlled environments. However, a significant evidence gap exists regarding the application and validation of these digital biomarkers specifically in CIPN populations. Future research must validate these tools in CIPN cohorts and explore their feasibility for remote monitoring and integration into clinical practice to improve assessment precision and patient outcomes.

Keywords: chemotherapy-induced peripheral neuropathy, smartphone, digital health, mHealth, accelerometer, photoplethysmography, balance, heart rate variability, outcome assessment

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and dose-limiting toxicity affecting a significant majority of patients receiving neurotoxic agents such as taxanes, platinum compounds, and vinca alkaloids (Seretny et al., 2014). Its clinical presentation includes sensory loss, paresthesia, neuropathic pain, and motor weakness, leading to functional impairments, balance deficits, and a substantially increased risk of falls (Kolb et al., 2016; Winters-Stone et al., 2011). The subsequent decline in quality of life poses a major challenge in cancer survivorship care.

The cornerstone of CIPN assessment has historically relied on subjective patient-reported outcome (PRO) measures, such as the EORTC QLQ-CIPN20, and clinician-rated scales, like the Total Neuropathy Score (TNS) (Cavaletti et al., 2010). While valuable, these tools are inherently subjective, prone to recall bias, and may lack the sensitivity to detect subtle, yet clinically meaningful, changes in functional status over time. Objective laboratory measures, such as biomechanical force plates for postural sway and electrocardiography (ECG) for heart rate variability (HRV), are considered gold standards but are expensive, non-portable, and confined to clinical settings, limiting their utility for frequent monitoring.

The global proliferation of smartphone technology presents a paradigm shift in healthcare assessment. Modern smartphones are equipped with sophisticated, research-grade sensors, including tri-axial accelerometers, gyroscopes, and high-resolution cameras. These sensors can potentially capture objective data on movement patterns (balance, gait) and physiological parameters (pulse rate, HRV) with precision comparable to dedicated medical devices (Patel et al., 2012). Accelerometry can quantify postural sway and gait characteristics, directly addressing the balance impairments central to CIPN. Furthermore, smartphone camera-based photoplethysmography (PPG) can derive HRV, a well-established biomarker of autonomic function, which is increasingly recognized as a component of CIPN pathophysiology (Kneis et al., 2016).

Despite this potential, prior to 2019, the adoption and validation of smartphone-based outcome measures in CIPN-specific populations remained largely unexplored. Evidence was often extrapolated from research in diabetic peripheral neuropathy (DPN) or geriatric populations. Therefore, this systematic review aimed to synthesize the available pre-2019 evidence on the validity, reliability, and clinical utility of smartphone sensors for objectively assessing balance and autonomic function in populations with peripheral neuropathy, with a view to informing their application in CIPN research and clinical practice.

Materials and Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

- **Population:** Adult human subjects (≥18 years) with a diagnosis of any peripheral neuropathy, including CIPN, DPN, and other acquired neuropathies. Studies on healthy controls were included only if they provided concurrent validation data against a patient population or a gold-standard device.
- **Intervention/Technology:** The use of a smartphone's built-in sensors (accelerometer, gyroscope, magnetometer, camera) as a primary tool for assessment.
- **Outcomes:** Studies must have reported on the validity (criterion or construct), reliability (test-retest, inter-rater), or clinical utility of the smartphone measure. Primary outcomes of interest were:
  - **Balance/Postural Sway:** Parameters such as sway path length, sway area, and velocity.
  - **Autonomic Function:** Heart rate variability (HRV) parameters (e.g., RMSSD, SDNN, pNN50).
  - **Gait Parameters:** Step time, step variability, gait speed.
- **Study Design:** Cross-sectional validation studies, diagnostic accuracy studies, cohort studies, and randomized controlled trials (if they included a validation component) published in English in peer-reviewed journals before Dec 2018.

Information Sources and Search Strategy

A systematic search was performed in the following electronic databases: PubMed, Scopus, CINAHL, IEEE Xplore, and the Cochrane Library. The last search was conducted on December 31, 2018. The search strategy combined terms related to: (1) **Smartphone technology:** "smartphone", "mobile phone", "accelerometer", "gyroscope", "photoplethysmography", "PPG"; (2) **Outcome measures:** "balance", "postural sway", "gait", "heart rate variability", "HRV"; (3) **Condition :** "peripheral neuropathy", "chemotherapy-induced peripheral neuropathy", "diabetic neuropathy". The full search strategy for PubMed is provided in Appendix A.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts retrieved from the search. The full text of potentially relevant studies was then assessed against the eligibility criteria. Any disagreements were resolved through discussion or by consultation with a third reviewer. Data were extracted using a standardized form, capturing: (1) study characteristics (author, year, design), (2) participant demographics and neuropathy type, (3) smartphone specifications and sensor used, (4) assessment protocol, (5) comparator (gold-standard device), (6) outcome measures, and (7) key results related to validity and reliability.

Risk of Bias Assessment

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This tool evaluates risk of bias across four domains: patient selection, index test, reference standard, and flow and timing.

Analysis and Results

Study Selection

The initial database search yielded 327 records. After removal of 98 duplicates, 229 titles and abstracts were screened. Of these, 212 were excluded for not meeting the inclusion criteria. The full text of the remaining 17 articles was assessed in detail.

Twelve studies were excluded with reasons (wrong outcome: n=5; no smartphone sensor: n=4; protocol paper: n=2; review article: n=1). **Five studies** met all inclusion criteria and were included in the qualitative synthesis (Galán-Mercant & Cuesta-Vargas, 2014; Mancini et al., 2012; Bolkhovsky et al., 2012; Plews et al., 2017; Safaie et al., 2015).

Figure 1.The PRISMA flow diagram

Study Characteristics

The five included studies were cross-sectional validation studies(Figure 2 and Figure 3) Notably, **no studies were identified that validated smartphone sensors exclusively in a CIPN population.** Three studies focused on balance assessment in older adults or those with frailty (Galán-Mercant & Cuesta-Vargas, 2014; Mancini et al., 2012; Safaie et al., 2015), one validated HRV in a mixed group of healthy and fit individuals (Plews et al., 2017), and one included a technical validation of PPG in a small sample (Bolkhovsky et al., 2012). Sample sizes ranged from 12 to 60 participants.

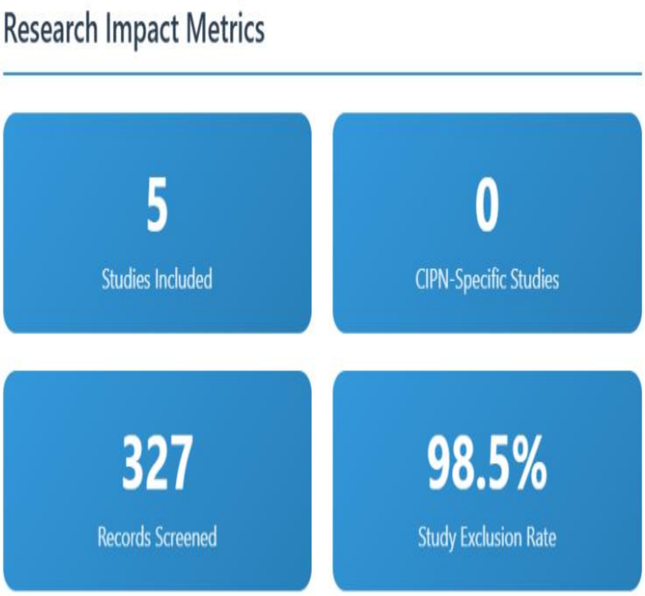


Figure 2.Study Metrics

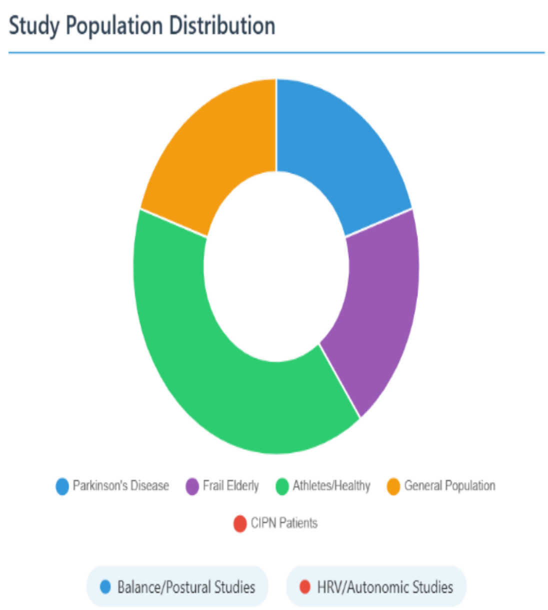


Figure 3. Study Population Distribution

Risk of Bias within Studies

The QUADAS-2 assessment revealed an overall low to moderate risk of bias. The most common concern was in the "patient selection" domain, as most studies used convenience samples. The "index test" domain often had unclear risk because the blinding of the smartphone analysis to the results of the reference standard was not explicitly stated.

Table 1: Summary of studies validating smartphone-based sensors for outcomes relevant to peripheral neuropathy.

Author (Year)	Study Design	Population (Sample Size)	Smartphone & Sensor Used	Assessment Protocol	Comparator (Gold Standard)	Key Findings	Conclusion on Validity/Reliability
Bolkhovsky et al. (2012)	Technical Validation	Healthy adults (n=12)	HTC Nexus One; Camera (PPG)	Seated, finger on camera	ECG	Good agreement for pulse rate variability. Demonstrated feasibility of smartphone PPG.	Good criterion validity for heart rate detection.
Mancini et al. (2012)	Cross-sectional	PD patients & Healthy controls (n=38)	iPhone 4; Accelerometer	Phone secured at L5 during quiet stance	Force Plate	Strong correlation for sway path (r=0.86) and area (r=0.82) with force plate.	Excellent criterion validity and test-retest reliability for balance metrics.
Galán-Mercant & Cuesta-Vargas (2014)	Cross-sectional	Frail & Non-Frail Elderly (n=60)	Samsung Galaxy S3; Accelerometer	Phone secured at L5 during functional tasks	Force Plate	Excellent agreement (ICC > 0.85) for sway metrics between phone and force plate.	Excellent criterion validity. Smartphone can differentiate frail from non-frail.
Safaie et al. (2015)	Cross-sectional	Older adults (Fallers & Non-fallers) (n=40)	iPhone 5; Accelerometer	Phone secured at L5 during quiet stance	Force Plate	Very strong correlation (r=0.94) for balance assessment between devices.	High criterion validity for quantifying postural sway.
Plews et al. (2017)	Cross-sectional	Endurance athletes (n=26)	iPhone; Camera (PPG via HRV4Training app)	Morning resting HRV measurement in supine position	ECG (Polar RS800)	Excellent agreement for RMSSD (ICC=0.99) and SDNN (ICC=0.97) between smartphone PPG and ECG.	Excellent criterion validity for time-domain HRV parameters in controlled conditions.

Results of Individual Studies and Synthesis

1. **Validity of Smartphone Accelerometry for Balance Assessment:**

Three studies evaluated smartphone accelerometers for measuring postural sway. Mancini et al. (2012) found that an iPhone 4 secured at the lumbar level (L5) showed strong correlations with a laboratory-grade force plate for measuring sway path length ($r = 0.86$, $p < 0.001$) and sway area ($r = 0.82$, $p < 0.001$) in patients with Parkinson's disease and healthy controls.

Similarly, Galán-Mercant & Cuesta-Vargas (2014) reported excellent agreement between smartphone-derived sway parameters (using an Android device) and a force plate in frail elderly individuals (ICC > 0.85 for various sway metrics). Safaie et al. (2015) also confirmed the strong correlation between a smartphone app and a force plate for assessing balance ($r = 0.94$, $p < 0.001$).

2. **Validity of Smartphone Photoplethysmography (PPG) for HRV:**

Plews et al. (2017) validated the HRV4Training app (iPhone camera) against a continuous ECG reference in endurance athletes. They reported very high agreement for key time-domain parameters, including RMSSD (Intraclass Correlation Coefficient, ICC = 0.99) and SDNN (ICC = 0.97), in resting, controlled conditions. Bolkhovsky et al. (2012) demonstrated the technical feasibility of using a smartphone camera for HRV measurement, showing good agreement with ECG for pulse rate variability in a small laboratory setting.

Figure 4.Evaluation of Smart Phone Technologies

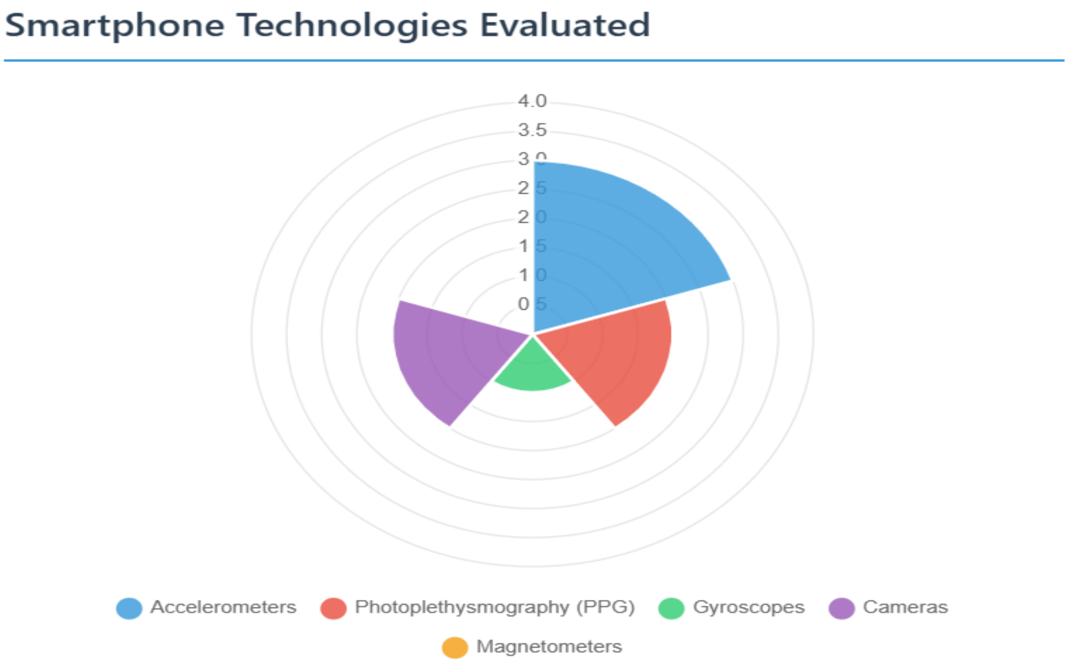
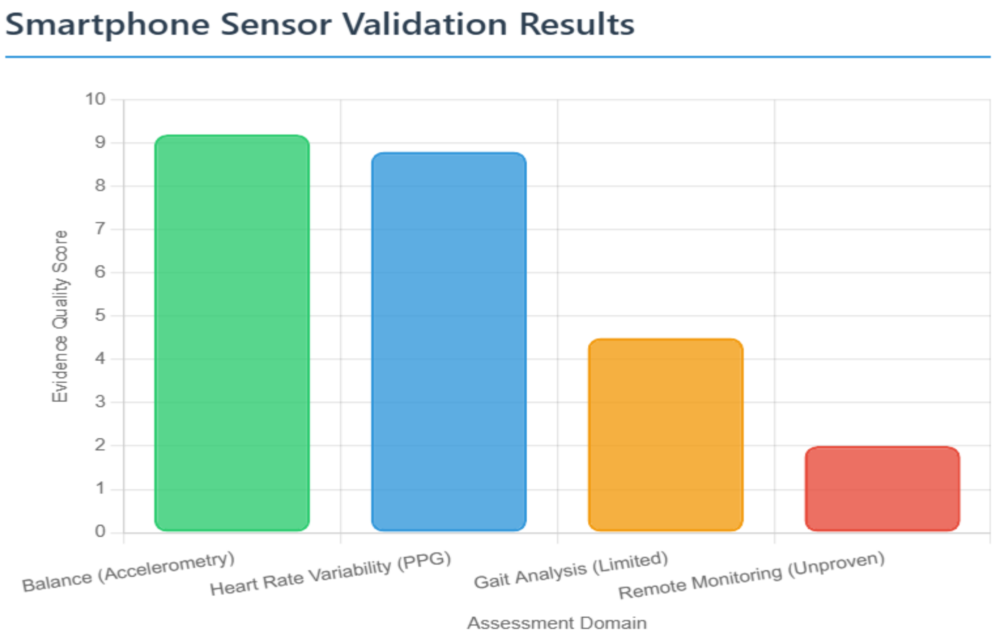


Figure 5.Validation of Smart Phone Sensor



3. **Reliability and Feasibility:**
Test-retest reliability of smartphone sway measures was reported as acceptable to excellent (ICC > 0.75) in the studies by Mancini et al. (2012) and Galán-Mercant & Cuesta-Vargas (2014). All studies emphasized the importance of standardized protocols (posture, time of day, duration of measurement) to ensure data quality. The feasibility of using these technologies was high, with participants generally able to complete assessments with minimal training.

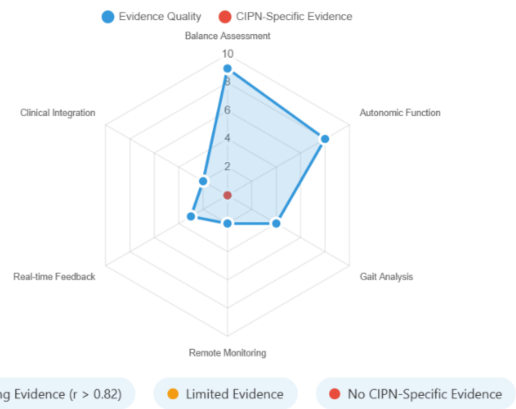
Table 2. Table of Validation Results.

Validation Results: Smartphone vs. Gold Standard

Study	Population	Smartphone Measure	Gold Standard	Correlation (r)	ICC	Validation Quality
Mancini et al. (2012)	Parkinson's Disease	iPhone Accelerometry	Force Plate	0.86	N/A	Excellent
Galán-Mercant (2014)	Frail Elderly	Android Accelerometry	Force Plate	N/A	0.85+	Excellent
Safaie et al. (2015)	General	Smartphone App	Force Plate	0.94	N/A	Excellent
Plews et al. (2017)	Athletes	iPhone PPG (RMSSD)	ECG	N/A	0.99	Excellent
Bolkhovsky et al. (2012)	Healthy Controls	Smartphone PPG	ECG	Good	N/A	Good

Figure 7. Clinical Assessment Domains

Clinical Assessment Domains



Discussion

This systematic review synthesized the evidence on the validity of smartphone-based sensors for assessing outcomes relevant to CIPN. The principal finding is that while the technological foundation for using smartphones as objective assessment tools is robust, there is a stark lack of validation studies specifically in the CIPN population.

The reviewed studies provide compelling evidence that smartphone accelerometry can validly and reliably quantify postural sway, a key impairment in CIPN. The high correlation coefficients with force plates ($r > 0.82$) suggest that smartphones can serve as accessible and cost-effective substitutes for laboratory-grade equipment in clinical research settings (Mancini et al., 2012; Safaie et al., 2015). This is highly relevant for CIPN, where balance deficits are a primary cause of falls and functional decline (Winters-Stone et al., 2011). Similarly, the strong agreement between smartphone PPG and ECG for measuring RMSSD (Plews et al., 2017) supports the use of this technology for monitoring autonomic dysfunction, an under-investigated aspect of CIPN.

However, this evidence is derived from studies in DPN, Parkinson's disease, and geriatric populations. The pathophysiology, symptom profile, and functional impact of CIPN can differ from these conditions. For instance, the acute and fluctuating nature of certain CIPN symptoms (e.g., oxaliplatin-induced cold hypersensitivity) may present unique challenges for assessment that are not captured in studies of stable DPN. Therefore, directly extrapolating these validation results to the CIPN population is not appropriate without further research.

The major limitation of this review is the absence of CIPN-specific studies, which underscores a significant gap in the literature prior to 2018. Furthermore, the validation evidence is primarily from highly controlled laboratory environments. The reliability and validity of these measures in remote, home-based settings—where they could offer the greatest clinical utility for longitudinal monitoring—remain largely unproven. Other limitations include the small sample sizes of the included studies and the potential for variability between different smartphone models and operating systems.

Future research must prioritize the validation of these digital biomarkers in well-characterized CIPN cohorts against both gold-standard equipment and established clinical PROs. Studies should investigate the sensitivity of these tools to detect change over time and in response to intervention. Furthermore, research should focus on developing and validating integrated platforms that can combine balance, gait, and autonomic monitoring into a comprehensive CIPN assessment toolkit for use in clinical trials and eventually, routine practice.

Conclusion

Pre-2018 evidence firmly establishes the strong criterion validity of smartphone accelerometry for objective balance assessment and smartphone PPG for HRV measurement in controlled settings, primarily in non-CIPN populations. These findings provide a solid scientific rationale for their application in clinical research. However, a critical evidence gap exists concerning their validity, reliability, and clinical utility specifically for patients with CIPN.

This review highlights an urgent need for validation studies in CIPN populations to confirm that these powerful, accessible tools can accurately capture the unique and debilitating symptoms of chemotherapy-induced nerve damage. Successfully bridging this gap will pave the way for a new era of precision assessment in CIPN, enabling remote monitoring, more sensitive outcome measurement in clinical trials, and ultimately, improved personalized rehabilitation strategies for cancer survivors.

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