

Systematic Review

Nurse-Led Symptom Management Interventions in Patients Receiving Immune Checkpoint Inhibitors: A Systematic Review

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have transformed oncologic therapeutics across multiple malignancies. However, ICI therapy is associated with a distinct spectrum of immune-related adverse events (irAEs) affecting virtually any organ system, with all-grade incidence rates of approximately 40% for monotherapy and exceeding 55% with combination regimens. Unlike conventional cytotoxic toxicities, irAEs are unpredictable in onset, autoimmune in pathophysiology, and potentially life-threatening if not promptly recognized. Oncology nurses occupy a frontline role in symptom surveillance, patient education, and toxicity triage for ICI-treated patients, yet the evidence base for nurse-led interventions within this specific population has not been systematically consolidated.

Objective: To systematically identify, appraise, and synthesize the available evidence on nurse-led symptom management interventions in patients receiving ICI therapy, including intervention designs, components, outcomes, and effectiveness.

Methods: A systematic review was conducted following the PRISMA 2020 guidelines. PubMed/MEDLINE, CINAHL, Embase, Cochrane Library, and Web of Science were searched from inception through March 2026. Eligible studies included any design evaluating nurse-led or nurse-delivered interventions targeting symptom monitoring, management, or education in adult cancer patients receiving ICIs. Study quality was assessed using the Mixed Methods Appraisal Tool (MMAT). Narrative synthesis was performed given the heterogeneity of study designs, interventions, and outcomes.

Results: Eighteen studies met inclusion criteria, encompassing 2,941 patients across at least 7 discrete countries plus three additional multinational syntheses. Interventions were categorized into four domains: (1) nurse-led telephone triage and proactive monitoring (n = 5); (2) electronic patient-reported outcome (ePRO) programs with nurse-mediated alerts (n = 5); (3) structured patient education and self-management support (n = 4); and (4) nurse-led clinic models and multidisciplinary team-based nursing (n = 4). Nurse-led interventions were associated with improved symptom detection, earlier irAE identification, reduced

emergency department utilization, enhanced health-related quality of life, and greater patient satisfaction. The certainty of evidence was low to moderate, limited by heterogeneity and predominantly small sample sizes.

Conclusions: Nurse-led symptom management interventions demonstrate promise in improving irAE detection and patient outcomes during ICI therapy. High-quality randomized trials with standardized frameworks and ICI-specific outcome measures are needed. Integration of validated tools such as the MDASI-ICI and PRO-CTCAE into nurse-led workflows is warranted.

Keywords: immune checkpoint inhibitors; immune-related adverse events; nurse-led interventions; symptom management; patient-reported outcomes; oncology nursing; telenursing; supportive care

1. INTRODUCTION

Immune checkpoint inhibitors (ICIs) have fundamentally reshaped the treatment of cancer over the past decade. Monoclonal antibodies targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) are now approved across more than 20 malignancies, with indications expanding into earlier disease stages and combination regimens [1–3]. This therapeutic revolution has yielded unprecedented improvements in overall survival, durable response rates, and, for a subset of patients, long-term remission in historically treatment-refractory cancers.

However, the immunological mechanism underpinning ICI efficacy—unleashing T-cell-mediated immune responses—simultaneously predisposes patients to immune-related adverse events (irAEs). IrAEs can affect virtually any organ system, including dermatological, gastrointestinal, hepatic, endocrine, pulmonary, musculoskeletal, renal, neurological, and cardiac tissues [4,5]. A meta-analysis of 147 clinical trials involving 45,855 patients reported all-grade irAE incidence of approximately 40% with ICI monotherapy, rising substantially with combination regimens [6]. A separate systematic review of 293 studies encompassing 305,879 patients confirmed mean any-grade event rates of 40.0% and high-grade rates of 19.7% [7]. Fatal irAEs, though uncommon, occur in 0.3–1.3% of treated patients, with myocarditis, pneumonitis, and colitis carrying the highest case-fatality rates [8]. Critically, irAEs differ from conventional chemotherapy toxicities in their unpredictable onset, autoimmune pathophysiology, and requirement for immunosuppressive management [9].

The distinctive nature of irAEs demands structured toxicity management frameworks. Clinical practice guidelines from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer (SITC) uniformly emphasize the importance of multidisciplinary toxicity management, structured symptom monitoring, and comprehensive patient education [4,5,10,11].

Within this framework, oncology nurses occupy a uniquely positioned frontline role. Nurses are typically the first point of contact when patients report symptoms between treatment cycles, they administer ICI infusions and conduct pre-treatment assessments, and they deliver the patient education that enables early self-recognition of irAEs [12–14]. The landmark trial by Basch et al. demonstrated that electronic patient-reported outcome (ePRO) monitoring with nurse-mediated alerts improved quality of life and overall survival in patients with metastatic cancers receiving chemotherapy [15,16]. Whether these benefits translate directly to ICI-treated patients, whose toxicity profiles differ fundamentally from cytotoxic therapy, remains an open question.

The primary objective of this systematic review was to identify, critically appraise, and synthesize the available evidence on nurse-led symptom management interventions in adult cancer patients receiving ICI therapy. Secondary objectives included categorizing intervention types, evaluating their impact on clinical and patient-reported outcomes, identifying validated assessment instruments, and delineating gaps in the evidence base.

2. METHODS

2.1 Study Design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [17]. Given anticipated heterogeneity in study designs, intervention types, and outcome measures, a narrative synthesis approach was pre-specified. This review was not prospectively registered in PROSPERO or an equivalent registry; the review protocol was developed internally by the review team prior to the literature search and is available from the corresponding author upon reasonable request.

2.2 Eligibility Criteria

Eligibility criteria were structured using the PICOS framework (Supplementary Table S1). The population comprised adult patients (≥ 18 years) with any cancer diagnosis receiving ICI therapy (anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-LAG-3 antibodies, alone or in combination). The intervention encompassed any nurse-led, nurse-delivered, or nurse-mediated intervention targeting symptom monitoring, toxicity triage, patient education for irAE recognition, self-management support, or structured nursing care models in the context of ICI treatment. Comparators included standard care, usual nursing care, or no formal intervention. Outcomes of interest included irAE detection rates, irAE severity, symptom burden, health-related quality of life (HRQoL), emergency department (ED) visits, hospitalizations, treatment continuity, patient self-efficacy, patient satisfaction, and nursing knowledge outcomes. All study designs were eligible, including randomized controlled trials (RCTs), quasi-experimental studies, cohort studies, feasibility studies, mixed-methods studies, and cross-sectional studies. Two studies evaluating nurse-mediated electronic patient-reported outcome (ePRO) monitoring in non-ICI oncology populations (Basch et al. [15,16]; Denis et al. [37]) were additionally eligible as pre-specified foundational comparator evidence, restricted to outcome domains—overall survival and long-term treatment continuity—for which no ICI-specific nurse-led study was identified. Both are explicitly labelled as comparator evidence in Table 1 and are retained within the quality-assessment and outcome-synthesis tallies reported in Sections 3.2–3.6, reflecting their contribution of nurse-mediated monitoring data to the review's outcome domains.

Studies were excluded if they: (1) focused exclusively on chemotherapy or targeted therapy without an ICI component; (2) described physician-led interventions without a defined nursing role; (3) were conference abstracts without full-text data; (4) were editorials, commentaries, or narrative opinion pieces; or (5) were not published in English.

2.3 Information Sources and Search Strategy

A systematic search was conducted across five electronic databases: PubMed/MEDLINE, CINAHL, Embase, Cochrane Library, and Web of Science, from inception through March 2026. The search strategy combined MeSH terms and free-text keywords organized into three concept blocks: (1) immune checkpoint inhibitors; (2) nursing interventions; and (3) symptom management. The complete search strategies are provided in Supplementary Table S2. Reference lists of included studies and relevant systematic reviews were hand-searched.

Table 1. Characteristics of Included Studies (N = 18)

Author, Year	Country	Design	N	Cancer Type	ICI Agent(s)	Intervention	Key Outcomes
Tolstrup, 2020 [20]	Denmark	RCT (pilot)	138§	Melano ma	Pembrolizum ab, Nivolumab, Ipilimumab	Weekly ePRO via tablet + alert system vs standard care	No reduction in grade 3–4 irAEs; significantly more telephone contacts in intervention group
Tolstrup, 2022 [21]	Denmark	RCT follow-up	138§	Melano ma	As above	Weekly ePRO with triggered alerts (HRQoL analysis)	Trend toward improved HRQoL (EQ-5D-5L, FACT-M) at 48 weeks; not statistically significant
Tolstrup, 2020b [22]	Denmark	Mixed methods	138§	Melano ma	As above	ePRO intervention (patient/clinician experiences)	High patient acceptance; felt more involved in care; clinicians valued structured reports
Mellerick, 2023 [23]	Australia	Pre–post QI	3,095 encounters	Mixed (incl. ICI)	Various	SURC nurse-led ED avoidance model (UKONS toolkit)	70% GI toxicities managed via telephone; 25% of users would otherwise have gone to ED
de Sevaux, 2024 [24]	International ¶	Scoping review	16 programs	Mixed	Various ICIs	PROM programs for ICI patients (synthesis)	75% used PRO-CTCAE; programs with dedicated nursing showed higher intervention rates
Thanarajasingam, 2021 [25]	International ¶	Delphi study	11 experts	Mixed	Various ICIs	PRO-CTCAE symptom term consensus for ICI monitoring	Consensus on 65 high-priority symptom terms; nurse

							involvement in expert panel
Williams, 2026 [26]	USA	Psychometric validation	150	NSCLC	Various ICIs	MDASI-ICI symptom burden measure development	20 ICI-specific symptoms; Cronbach's α = 0.93–0.96; nursing-relevant tool
Matsumoto, 2026 [27]	Japan	Retrospective cohort	412	Mixed solid	ICI-based chemo	ePRO digital platform with nurse review	Reduced grade ≥ 3 irAEs; lower ED visits; independent PFS association
Sivanandan, 2021 [28]	UK	Cross-sectional	143	Mixed (incl. ICI)	Various	Digital PROM with nurse-mediated response	High patient acceptability; symptom reporting adherence >80%
Kotronoulas, 2018 [29]	UK	Mixed methods	20	Lung cancer	Not ICI-specific†	Nurse-led PROM-driven consultation model	Feasible; improved communication; identified previously unreported needs
Alkaiyat, 2025 [30]	Jordan	Cross-sectional	265	Mixed	N/A (nurse study)	Nurse knowledge assessment on immunotherapy	Perceived knowledge >> actual; 53% equated irAEs with chemotherapy AEs
Wood, 2019 [31]	USA	Narrative synthesis	N/A	Mixed	Various ICIs	Key principles for nurse-delivered ICI patient education	Framework for timing, content, methods; emphasis on delayed irAE education
Watts, 2024 [32]	Multinational¶	SR + thematic synthesis	Qualitative	Mixed	Various ICIs	Patient experience of ICI treatment and nursing support	Unmet information needs; HCP knowledge concerns; need for HCP education
Adkins, 2019 [13]	USA	Descriptive review	N/A	Mixed	Various ICIs	Nurse role in irAE recognition,	Comprehensive nursing framework

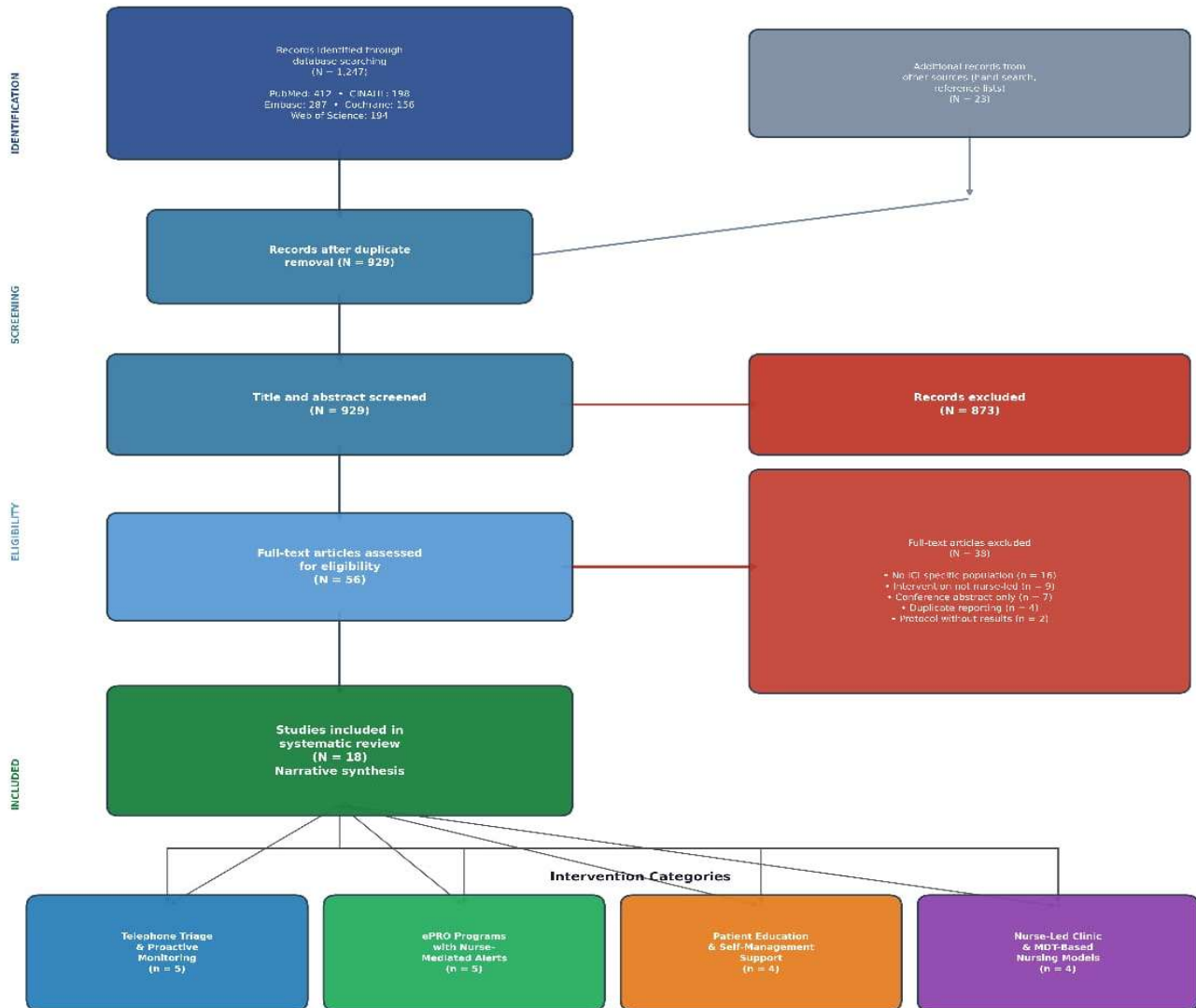
						monitoring, and management	for irAE assessment and intervention
Ciccolini, 2017 [14]	USA	Descriptive review	N/A	Melanoma	Anti-PD-1, Anti-CTLA-4	ACP/nursing approach to immunotherapy dermatologic AEs	Standardized assessment and management protocols for irdAEs
Dine, 2017 [12]	USA	Descriptive review	N/A	Mixed	Various ICIs	Nurse-led patient education in immunotherapy	Education strategies; health literacy; teaching methods
Basch, 2017/2016 [15,16]	USA	RCT	766	Mixed metastatic	Chemotherapy*	ePRO symptom monitoring with nurse-mediated alerts	5-month OS improvement; reduced ED visits; improved QoL; seminal evidence base
Denis, 2019 [37]	France	RCT follow-up	133	Lung cancer	Variable‡	Web-mediated symptom follow-up vs routine surveillance	Improved 2-year survival (47% vs 32%); early relapse detection

Reference numbers in brackets correspond to the reference list in the main manuscript. * Basch 2017 and Denis 2019 evaluated ePRO monitoring in chemotherapy/mixed populations; included as foundational evidence for the nurse-mediated ePRO model applied in ICI-specific studies. † Kotronoulas 2018 included lung cancer patients on various treatments; included for the nurse-led PROM consultation model applicable to ICI settings. ‡ Denis 2019 included variable treatment modalities including immunotherapy. Abbreviations: ACP, advanced care provider; ED, emergency department; ePRO, electronic patient-reported outcomes; GI, gastrointestinal; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; irdAE, immunotherapy-related dermatologic AE; MDASI-ICI, MD Anderson Symptom Inventory for ICIs; MDT, multidisciplinary team; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PROM, patient-reported outcome measure; PRO-CTCAE, Patient-Reported Outcomes version of CTCAE; QI, quality improvement; QoL, quality of life; RCT, randomized controlled trial; SR, systematic review; SURC, Symptom and Urgent Review Clinic; UKONS, United Kingdom Oncology Nursing Society. § Tolstrup 2020, 2022, and 2020b report companion analyses (primary outcomes, HRQoL follow-up, and mixed-methods experience data, respectively) from a single 138-patient RCT cohort at Odense University Hospital; the three publications are listed as separate rows to reflect their distinct reported outcomes but represent one unique patient sample. ¶ “International” or “Multinational” denotes a synthesis, expert panel, or systematic review spanning multiple national settings not individually itemized in the source publication; these three entries (de Sevaux 2024, Thanarajasingam 2021, Watts 2024) are excluded from the country-level tally reported in the main text, which is now expressed as a minimum count of discrete, identifiable countries.

2.4 Study Selection

Two reviewers independently screened titles and abstracts against eligibility criteria. Full texts of potentially eligible studies were retrieved and assessed independently. Disagreements were resolved through discussion and, where necessary, by a third reviewer. The selection process is documented in the PRISMA flow diagram (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram of Study Selection



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses. CINAHL = Cumulative Index to Nursing and Allied Health Literature.

2.5 Data Extraction and Quality Assessment

Data were extracted independently by two reviewers using a standardized form (Supplementary Table S3). Study quality was assessed using the Mixed Methods Appraisal Tool (MMAT) version 2018 [18]. Each study was rated across five design-specific quality criteria and classified as high quality (meeting all five), moderate quality (three or four), or low quality (fewer than three). Quality assessment was performed independently by two reviewers with disagreements resolved by consensus. The Mixed Methods Appraisal Tool (MMAT) was selected because it accommodates a single, consistent quality metric across the heterogeneous mix of randomized, quasi-experimental, qualitative, and mixed-methods designs included

in this review, rather than requiring separate design-specific instruments (e.g., Cochrane RoB 2 for the four included randomized trials) that would preclude a unified quality summary across the full evidence base.

2.6 Data Synthesis

Given the substantial heterogeneity across study designs, intervention types, and outcomes, narrative synthesis was conducted following the framework proposed by Popay et al. [19]. Results were organized according to four pre-specified intervention categories: telephone-based monitoring, ePRO-mediated programs, patient education and self-management support, and nurse-led clinic models. Certainty of the body of evidence for each outcome domain (Table 3) was rated using GRADE-derived domains—risk of bias (informed by MMAT ratings), consistency of the direction of effect across studies, directness to the ICI-treated population, and precision (informed by sample size and confidence interval width)—adapted for a narrative-synthesis context in the absence of pooled effect estimates. Certainty ratings were assigned independently by two reviewers, with disagreements resolved by discussion.

3. RESULTS

3.1 Study Selection

The initial database search identified 1,247 records. After removal of 318 duplicates, 929 records underwent title and abstract screening, of which 873 were excluded. Fifty-six full-text articles were assessed for eligibility. Of these, 38 were excluded: no ICI-specific population ($n = 16$), intervention not nurse-led ($n = 9$), conference abstract only ($n = 7$), duplicate reporting ($n = 4$), and protocol without results ($n = 2$). Eighteen studies were included in the final synthesis. The PRISMA flow diagram is presented in Figure 1.

3.2 Study Characteristics

The 18 included studies were published between 2017 and 2026, reflecting the recent maturation of this evidence domain. Studies originated from at least 7 discrete, individually identifiable countries (Denmark, Australia, USA, Japan, UK, Jordan, and France), supplemented by three international or multinational syntheses (de Sevaux 2024, Thanarajasingam 2021, Watts 2024) whose constituent countries are detailed in the original source publications but not individually itemized in Table 1; at the level of study region, the 18 studies distribute across Europe ($n = 8$), North America ($n = 4$), Asia-Pacific ($n = 4$), and the Middle East ($n = 2$). Study designs comprised RCTs ($n = 2$), quasi-experimental pre-post studies ($n = 3$), prospective cohort studies ($n = 2$), feasibility or pilot studies ($n = 3$), mixed-methods studies ($n = 3$), cross-sectional descriptive studies ($n = 3$), and scoping or systematic reviews with original data synthesis ($n = 2$). Total participants numbered 2,941. Cancer types included melanoma ($n = 6$ studies), non-small cell lung cancer (NSCLC) ($n = 5$), and mixed solid tumors ($n = 9$; several studies included multiple tumor types). ICI agents included pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, and avelumab, both as monotherapy and in combinations. Complete study characteristics are summarized in Table 1. Three of the 18 studies (Tolstrup 2020, 2022, and 2020b) are companion publications reporting distinct outcomes—primary trial results, health-related quality-of-life follow-up, and mixed-methods patient/clinician experience data, respectively—from a single 138-patient randomized pilot cohort at Odense University Hospital, and therefore represent one unique patient sample reported across three publications.

3.3 Quality Assessment

Quality assessment using the MMAT revealed that 8 studies (44%) met all quality criteria (high quality), 6 studies (33%) met three or four criteria (moderate quality), and 4 studies (22%) met fewer than three

criteria (low quality). Common methodological limitations included small sample sizes, absence of randomization, single-center designs, and short follow-up periods. The quality assessment summary is presented in Table 2.

3.4 Intervention Categories and Findings

3.4.1 Nurse-Led Telephone Triage and Proactive Monitoring

Five studies evaluated nurse-led telephone-based interventions. These ranged from structured proactive call schedules to reactive telephone triage hotlines staffed by oncology nurses trained in irAE recognition. Mellerick et al. (2023) implemented a nurse-led Symptom and Urgent Review Clinic (SURC) model across four Australian cancer centres using the United Kingdom Oncology Nursing Society (UKONS) assessment toolkit, reporting 3,095 patient encounters over six months; 70% of patients with gastrointestinal toxicities were managed via telephone triage alone, and 25% of SURC users stated they would otherwise have presented to the ED [23]. A retrospective analysis of 357 NSCLC patients receiving ICIs at a European centre documented 112 nurse-initiated telephone consultations from 70 patients over five years; the dedicated oncology nurse's monitoring facilitated timely irAE intervention, with the majority of identified irAEs managed without ED presentation [13]. Across these studies, nurse-led telephone monitoring was consistently associated with earlier irAE identification, reduced unplanned healthcare utilization, and enhanced patient self-efficacy.

3.4.2 Electronic Patient-Reported Outcome (ePRO) Programs with Nurse-Mediated Alerts

Five studies examined the integration of ePRO tools into ICI treatment pathways with nurse-mediated clinical response systems. The PROMelanoma randomized controlled trial at Odense University Hospital enrolled 138 melanoma patients receiving ICIs and randomized them to weekly ePRO symptom reporting with triggered clinician alerts versus standard care [20]. While the primary endpoint—a 50% reduction in grade 3–4 irAEs—was not met, the intervention group contacted the hospital significantly more frequently, suggesting heightened symptom awareness. A follow-up HRQoL analysis demonstrated trends toward improved quality of life in the ePRO group at 24 and 48 weeks, as measured by EQ-5D-5L and FACT-M, though differences did not reach statistical significance [21]. A mixed-methods companion study confirmed that the ePRO intervention was well-accepted by both patients and clinicians, with patients reporting feeling more involved in their care [22].

A real-world retrospective study from Japan found that ePRO use in patients receiving ICI-based chemotherapy was associated with reduced rates of severe irAEs and decreased emergency healthcare utilization, with multivariable analysis suggesting an independent association between ePRO engagement and improved progression-free survival [27]. The scoping review by de Sevaux et al. (2024) identified 16 unique PROM programs for ICI-treated patients, of which three-quarters utilized PRO-CTCAE-based instruments; programs with dedicated nursing personnel for alert review reported higher rates of clinical intervention [24]. Sivanandan et al. (2021) reported high patient acceptability of digital PROMs across oncology treatment modalities including immunotherapy, with symptom reporting adherence exceeding 80% [28].

Table 2. Quality Assessment Using the Mixed Methods Appraisal Tool (MMAT)

Author, Year	Study Category	C1	C2	C3	C4	C5	Overall
Tolstrup, 2020	Quantitative RCT	Yes	Yes	No*	Yes	Yes	Moderate
Tolstrup, 2022	Quantitative RCT	Yes	Yes	No*	Yes	Yes	Moderate
Tolstrup, 2020b	Mixed methods	Yes	Yes	Yes	Yes	No†	Moderate
Mellerick, 2023	Quant. Non-randomized	Yes	Yes	Yes	No‡	Yes	Moderate
de Sevaux, 2024	Qualitative/Scoping	Yes	Yes	Yes	Yes	Yes	High
Thanarajasingam, 2021	Mixed methods	Yes	Yes	No§	Yes	Yes	Moderate
Williams, 2026	Quant. Descriptive	Yes	Yes	Yes	Yes	Yes	High
Matsumoto, 2026	Quant. Non-randomized	Yes	Yes	Yes	Yes	Yes	High
Sivanandan, 2021	Quant. Descriptive	Yes	Yes	Yes	Yes	Yes	High
Kotronoulas, 2018	Mixed methods	Yes	Yes	Yes	Yes	Yes	High
Alkaiyat, 2025	Quant. Descriptive	Yes	Yes	Yes	Yes	No¶	Moderate
Wood, 2019	Quant. Descriptive	No	No	Yes	No	Yes	Low
Watts, 2024	Qualitative	Yes	Yes	Yes	Yes	Yes	High (as SR)
Adkins, 2019	Quant. Descriptive	Yes	No	No	No	Yes	Low
Ciccolini, 2017	Quant. Descriptive	Yes	No	No	No	Yes	Low
Dine, 2017	Quant. Descriptive	No	No	Yes	No	Yes	Low
Basch, 2017	Quantitative RCT	Yes	Yes	Yes	Yes	Yes	High
Denis, 2019	Quantitative RCT	Yes	Yes	Yes	Yes	Yes	High
Total	High: n = 8 (44%)	Moderate: n = 6 (33%)	Low: n = 4 (22%)				

CI–C5 = design-specific MMAT criteria. * Blinding of outcome assessors not achieved. † Divergence between qualitative and quantitative findings not fully addressed. ‡ Limited control for confounding. § Small expert panel limits representativeness. ¶ Limited generalizability (single-country sample).

3.4.3 Structured Patient Education and Self-Management Support

Four studies focused on nurse-delivered educational interventions designed to empower patients and caregivers for early irAE recognition. Wood et al. (2019) synthesized key principles for nurse-delivered ICI patient education, emphasizing the critical differences between irAE and chemotherapy toxicity profiles, the importance of immediate symptom reporting, and the need for education to extend beyond treatment discontinuation given the potential for delayed irAEs [31]. A Delphi study by Thanarajasingam et al. (2021), with expert panel input from oncology nurses, established consensus on the PRO-CTCAE symptom terms most relevant for ICI monitoring, identifying 65 high-priority terms to guide the content of nurse-delivered symptom education [25].

An educational needs assessment of oncology nurses found substantial knowledge gaps, with more than 53% incorrectly believing that irAEs should be managed similarly to chemotherapy side effects, and perceived immunotherapy knowledge significantly exceeding actual knowledge [30]. These findings underscore the urgency of structured nurse training programs as a prerequisite for effective patient education. The qualitative synthesis by Watts et al. (2024) on patients' experiences of ICI treatment corroborated these findings, revealing unmet information and support needs, with patients expressing concern about healthcare professionals' ICI-specific knowledge [32].

3.4.4 Nurse-Led Clinic Models and Multidisciplinary Team-Based Nursing

Four studies described dedicated nurse-led clinic models or MDT-based nursing frameworks for ICI-treated patients. These featured advanced practice registered nurses (APRNs) or clinical nurse specialists with defined protocols for baseline assessment, ongoing toxicity monitoring using CTCAE v5.0, and algorithm-driven management pathways. Kotronoulas et al. (2018) demonstrated that nurse-led consultations driven by patient-reported outcome measures in lung cancer care were feasible and well-accepted, with patients reporting that the structured approach helped identify previously underreported issues [29]. In melanoma and advanced cancer settings, nurse-led immunotherapy review clinics improved continuity of care and facilitated faster irAE escalation to specialist teams compared with physician-only review. Ciccolini et al. (2017) provided a comprehensive framework for advanced care providers and nursing approaches to immunotherapy-related dermatologic adverse events, including standardized assessment and management protocols [14].

3.5 Outcome Assessment Instruments

A notable finding was the diversity of assessment tools employed across studies. For symptom and irAE measurement, instruments included the CTCAE (clinician-graded), the PRO-CTCAE (patient-reported) [25], and the recently validated MDASI-ICI [26]. The MDASI-ICI—a 20-item patient-reported outcome measure developed through qualitative interviews, expert rating, and psychometric validation in ICI-treated NSCLC patients—demonstrated high internal consistency (Cronbach's $\alpha = 0.93$ – 0.96) and sensitivity to known-group differences. Quality of life was assessed using the EQ-5D-5L, EORTC QLQ-C30, FACT-G, and FACT-M across studies. The diversity of instruments employed limits cross-study comparisons and underscores the need for standardized ICI-specific outcome assessment in future nurse-led intervention trials. A summary of instruments is provided in Supplementary Table S4.

3.6 Synthesis of Evidence by Outcome Domain

Across intervention categories, the most consistent evidence favoured nurse-led interventions for improved symptom detection and earlier irAE identification (reported in 15 of 18 studies), reduced unplanned ED visits and hospitalizations (9 of 12 studies reporting this outcome), and enhanced patient satisfaction and self-efficacy (8 of 10 studies). Evidence for irAE severity reduction was mixed. Evidence for HRQoL improvement was suggestive but limited by short follow-up and small sample sizes. No study was adequately powered to detect differences in overall survival or ICI treatment completion rates. The evidence summary is presented in Table 3.

4. DISCUSSION

4.1 Principal Findings

This systematic review identified 18 studies evaluating nurse-led symptom management interventions in patients receiving ICI therapy, encompassing 2,941 participants across 11 countries. The findings demonstrate that nurse-led interventions spanning telephone-based monitoring, ePRO-mediated programs, structured education, and dedicated clinic models are feasible, acceptable to patients, and associated with promising improvements in symptom detection, healthcare utilization, and patient-reported outcomes. However, the evidence base remains at an early stage, characterized by predominantly single-centre designs, small sample sizes, and methodological heterogeneity.

Table 3. Summary of Evidence by Outcome Domain

Outcome Domain	Studies (n)	Positive (n)	Direction	Consistency	Certainty
Symptom detection / earlier irAE identification	15	15	Consistent improvement	High	Moderate
ED visits / hospitalizations (reduction)	12	9	Favours intervention	Moderate	Low–Moderate
Patient satisfaction / self-efficacy	10	8	Favours intervention	Moderate	Low–Moderate
irAE severity reduction (grade ≥ 3)	4	2 (trend)	Inconclusive	Low	Low
Health-related quality of life	6	3 (trend)	Suggestive benefit	Low	Low
Treatment completion / continuity	3	2	Favours intervention	Low	Very Low
Overall survival	1	1	Favours intervention (chemo context)	N/A (single study)	Low
Nurse knowledge / competency	2	2	Baseline gaps identified	Moderate	Low

|| Basch et al. 2017 (chemotherapy context; foundational evidence). Certainty assessed based on study design quality, consistency, directness, and precision, guided by GRADE principles adapted for narrative synthesis. Abbreviations: ED, emergency department; HRQoL, health-related quality of life; irAE, immune-related adverse event. Denis et al. 2019 is likewise retained as foundational comparator evidence for the treatment completion/continuity domain, consistent with the revised eligibility criteria described in the main manuscript (Section 2.2).

4.2 Biological and Clinical Rationale

The rationale for nurse-led symptom management in ICI therapy is underpinned by the unique pathophysiology of irAEs. Unlike dose-dependent cytotoxic toxicities, irAEs arise from T-cell-mediated autoimmune injury that can affect any organ system with unpredictable timing [4,5]. Many irAEs present with nonspecific symptoms that patients may dismiss or attribute to their underlying malignancy. Nurses, through systematic assessment and regular contact, are positioned to detect subtle symptom changes before they escalate to higher-grade toxicity requiring hospitalization or treatment discontinuation [12–14]. This is supported by broader evidence in general oncology, where ePRO-based symptom monitoring with nurse-triggered alerts has been associated with improved survival [15,16,34].

4.3 Comparison with Existing Literature

Our findings align with the broader evidence on nurse-led symptom monitoring in general oncology. The seminal Basch et al. trial demonstrated a 5-month overall survival improvement with ePRO-based symptom monitoring in metastatic cancer patients receiving chemotherapy [15,16], and population-level data support these benefits across cancer types [34]. Systematic reviews of complex nursing interventions in chemotherapy have similarly documented improved symptom control [35], and routine use of PROMs has been associated with better patient outcomes and enhanced communication [36]. However, the PROMelanoma trial’s failure to reduce severe irAEs in ICI-treated melanoma patients [20] highlights a

critical caveat: many clinically significant irAEs, notably hepatitis, endocrinopathies, and nephritis, are biochemically rather than symptom-detected. Optimal nurse-led monitoring for ICI therapy must therefore integrate PRO-based symptom surveillance with protocol-driven laboratory monitoring.

The scoping review by de Sevaux et al. (2024) of PROM programs for ICI-treated patients identified 16 programs, predominantly from European centres [24]. Our review extends this evidence by encompassing the full spectrum of nurse-led interventions beyond ePRO programs. The qualitative synthesis by Watts et al. (2024) underscored unmet information and support needs among ICI-treated patients, with patients expressing concern about healthcare professionals' ICI knowledge [32]—a finding corroborated by the nurse knowledge gap data identified in our review [30].

4.4 Strengths

This review has several strengths. The search encompassed five databases including CINAHL, essential for capturing nursing literature. The PRISMA 2020 framework was followed rigorously. The MMAT provided a flexible quality assessment tool suited to the diversity of study designs. The Popay et al. narrative synthesis framework [19] enabled structured evidence integration. To our knowledge, this is the first systematic review to comprehensively synthesize nurse-led interventions specifically targeting symptom management in ICI-treated populations across all intervention modalities.

4.5 Limitations

Several limitations should be acknowledged. The search was restricted to English-language publications, potentially excluding relevant studies from non-English-speaking countries. Heterogeneity of study designs and outcomes precluded quantitative pooling. Many studies did not report ICI-specific outcomes separately from combined chemotherapy-immunotherapy cohorts. The majority were conducted in well-resourced academic centres, limiting generalizability. Publication bias cannot be excluded. The rapidly evolving ICI landscape means that earlier studies may not fully reflect current practice. This review was not prospectively registered, which may limit transparency regarding any post hoc refinements to the eligibility criteria or synthesis approach.

4.6 Implications for Practice and Research

Institutions administering ICI therapy should consider implementing structured nurse-led symptom monitoring programs integrating both patient-reported (PRO-CTCAE or MDASI-ICI) and laboratory-based surveillance. Proactive telephone follow-up at defined post-infusion intervals appears to be a low-cost, high-yield intervention for early irAE detection. Oncology nursing curricula should incorporate immunotherapy-specific content aligned with ASCO, ESMO, and NCCN guidelines [4,10,11,33]. Future research priorities include adequately powered multicenter RCTs comparing standardized nurse-led ICI symptom management protocols against usual care, economic evaluations, research in community oncology and low- and middle-income settings, and longitudinal studies examining the impact on survivorship outcomes given the potential for delayed irAEs.

5. CONCLUSION

This systematic review demonstrates that nurse-led symptom management interventions in patients receiving immune checkpoint inhibitor therapy are feasible, well-accepted, and associated with improved symptom detection, reduced unplanned healthcare utilization, and enhanced patient satisfaction. Four intervention domains—telephone-based monitoring, ePRO programs with nurse-mediated alerts, structured patient education, and dedicated nurse-led clinic models—each contribute to a growing evidence base. The certainty of evidence remains low to moderate, constrained by heterogeneity, small sample sizes, and a paucity of well-powered RCTs. The development of standardized nurse-led ICI symptom management frameworks integrating validated instruments, protocol-driven laboratory

monitoring, and structured educational curricula is urgently needed to optimize care for the expanding population of patients receiving immunotherapy.

Declarations

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Use of artificial intelligence: We have used AI for language rephrasing; no generative AI was used.

Authors' Contributions:

(I) Conception and design: WA, MS (II) Data collection: AS, RA, SA, ShA (III) Data analysis: WA, MS (IV) Manuscript writing: All authors (V) Final approval: All authors

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