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A systematic review of qualitative research

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Experience of patients considering or using checkpoint inhibitors in cancer treatment: a systematic review of qualitative research

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ABSTRACT

Increasing numbers of patients with cancer are considering or undergoing immunotherapy, however, little is known about patients' perspectives on this treatment. We undertook a systematic review for use by clinicians and researchers, consolidating published qualitative research studies on patient experience of checkpoint inhibitor therapy. A search of Medline, Embase, and PsycINFO was carried out for publications in English to 30 June 2022. Publications were selected if they reported a qualitative study of patient experience with checkpoint inhibitor therapy for cancer, either by patients or their families or carers. Quality was appraised using the Johanna Briggs Institute quality assessment tool for qualitative studies. A thematic synthesis was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standard was followed. We identified 17 eligible studies published between 2017 and 2022, 9 using mixed methods, and 8 solely using qualitative methods. Most studies reported on the experiences of patients with advanced stage melanoma and were using the earliest approved checkpoint inhibitors for cancer therapy. Studies met most formal quality criteria but varied in the extent of their qualitative explorations of data; some mixed methods studies had limited reporting of qualitative results. Through thematic synthesis, we categorized study findings into four domains: (1) treatment decision-making; (2) success with immunotherapy; (3) treatment-related adverse events (AEs); and (4) quality of life on immunotherapy. Our review identified several areas with potential for improving the care system. These include, for example: routinely linking patients to peers who have experienced this therapy; improving the capacity of patients and carers to identify and report AEs faster; and supporting patients and carers to live with changed circumstances after successful treatment. Most studies focused on patients who had successful treatment, effectively excluding those who do not respond or who discontinue due to serious side effects; future research targets are suggested.

INTRODUCTION

Over the past decade, the rapid development of immunotherapy and its effectiveness in improving patient survival has led to its emergence as a promising mainstay treatment for cancer care alongside chemotherapy and radiation therapy.[1] A recent study found the estimated percentage of patients with advanced stage cancer in the USA *potentially* eligible for the most common immunotherapy, checkpoint inhibitors, increased from 1.5% in 2011 to 43.6% in 2018.[2] As at February 2023, there are a total of nine Food and Drug Administration-approved checkpoint inhibitors available for use in cancer treatment.[3] Despite its efficacy in treating malignancies such as melanoma, the immune enhancing action of checkpoint inhibitors has associated adverse effects that can be severe and widespread.[4] Given the relative novelty of this therapy, we are still learning how patients experience it.

Clinical reporting by investigative practitioners tends to principally focus on patient mortality.[4] Safety or tolerability of cancer treatments in clinical trials are typically reported using items from the US National Cancer Institute's Common Terminology Criteria for Adverse Events.[5] Other measures of patient experience are less frequently considered, leading to a potential underestimation of adverse experiences.[6–8] This problem is well-established when reporting on cancer patients treated with chemotherapy and radiotherapy,[9 10] and the same pattern can be anticipated with immunotherapy,[11 12] especially as some types of negative experiences are unique to this treatment.

Patients' experiences of healthcare are subjective and can be influenced by many factors including the patient's health, emotional state and intrinsic preferences.[13] A number of recent clinical trials have incorporated patient-reported outcome measures (PROMs) when evaluating cancer

therapeutics.[9 14] PROMs evolved as a tool to evaluate patient symptoms in treatment trials, as a measure of quality of life (QoL).[15] The concept of QoL for a patient with cancer extends beyond health-related outcomes, however, as it can also be impacted by factors such as emotional stress or financial burden.[16] This broader perspective is often missing in studies of immunotherapy patients.[17]

To facilitate robust understanding, many types of research are required on patient experiences with checkpoint inhibitors. Experience of care may be better understood by using qualitative research methods, such as interviews and focus groups.[13] Further, patient experience can be reported not only by the ill individual, but also by caregivers who experience the whole process of undergoing treatment with them.[18] The perspectives of a patient's carer may be particularly valuable in instances in which the patient is unable to personally report their experience due to poor health.[19]

Recent studies have provided insights into various aspects of cancer patient experience with immunotherapies including preconceptions of treatment,[20] health-related outcomes reported by patients[4 21 22] and by carers.[15] Other studies have focused on developing immunotherapy-specific measures of adverse events (AEs).[12] As yet no systematic review has consolidated the qualitative evidence on patient experience of checkpoint inhibitors. Our systematic review aims to fill that gap, providing an overview of this literature for clinicians and researchers and identifying issues of potential relevance to the care system.

METHODS

The protocol for this study was registered with PROSPERO 2021 CRD42021248427.[23]

Approach to methodology

The authors drew on the research paradigms of interpretivism and pragmatism[24 25] in purpose-designing methods for engaging with primary qualitative data. The aim was to produce patient-reported knowledge of immunotherapy experience from the literature through interpretation of themes across the selected papers; a pragmatist, problem-solving approach was used to achieve consensus in quality appraisal rather than applying rigid methodological frameworks. The author team comprised early career and experienced researchers across clinical practice, social science, health systems research and qualitative and quantitative methods. Team members shared interests in producing translational evidence that would help clinicians improve care of patients receiving immunotherapy and providing foundations for qualitative researchers considering future research in the area.

Search strategy

Three databases were searched; Medline, Embase, and PsycInfo. Blocks of keywords and medical subject headings representing: (1) checkpoint inhibitor immunotherapies; (2) cancer; (3) qualitative research; and (4) patient experience or family experience were used. Online supplemental appendix A details search terms for each database. A snowballing strategy was employed, searching for eligible papers in the reference lists of the included papers. Final searches were conducted in late July 2022, for papers published on or before 30 June 2022.

Paper selection

Following removal of duplicates, references were screened based on the inclusion and exclusion criteria. Inclusion criteria were: patients with cancer; patients have received, or are receiving or considering checkpoint inhibitor therapy; qualitative data obtained through qualitative or mixed-methods studies (eg, interviews, focus groups, surveys/questionnaires with open-ended questions, ethnography, other method identifying itself as qualitative research such as formal personal narratives); experiences or outcomes reported by patient or patient's family or caregiver; empirical primary data reported; and report peer-reviewed. Exclusion criteria were: gray literature; no abstract available; posters; conference presentations; claimed qualitative method but not considered to be qualitative by authors; and not in English language.

Review of titles and abstracts produced a shortlist of papers for full-text review; in both steps, at least two members of the study team (RY and one of GA, KL, or BNGE) independently reviewed each paper, with discrepancies in inclusion decisions adjudicated through group discussion and consensus. If multiple papers were found studying the same patients, a consensus decision was made as to whether they constituted the same or separate studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement for systematic reviews was followed[26]; the completed checklists can be found in online supplemental appendix B.

Data extraction

Eligible papers were uploaded to the Rayyan web-tool[27] from EndNote X9.[28] For each eligible paper two members of the study team (RY and GA) independently abstracted the following data: country, year of publication, year of study, study aims, baseline characteristics of study population, cancer type and stage, treatment details, qualitative methodology, perspective of experience reported, patient experience themes reported and summary findings. Discrepancies were reviewed and adjudicated by consensus.

Quality appraisal

Included studies were assessed using the Johanna Briggs Institute (JBI) Checklist for Qualitative Research.[29] Appraisal was conducted by two reviewers (RY and KL) for all papers, with discrepancies and ambiguities resolved by consensus. As outlined by JBI, the aim of quality appraisal was to assess the extent to which each paper presented a robust methodological approach and

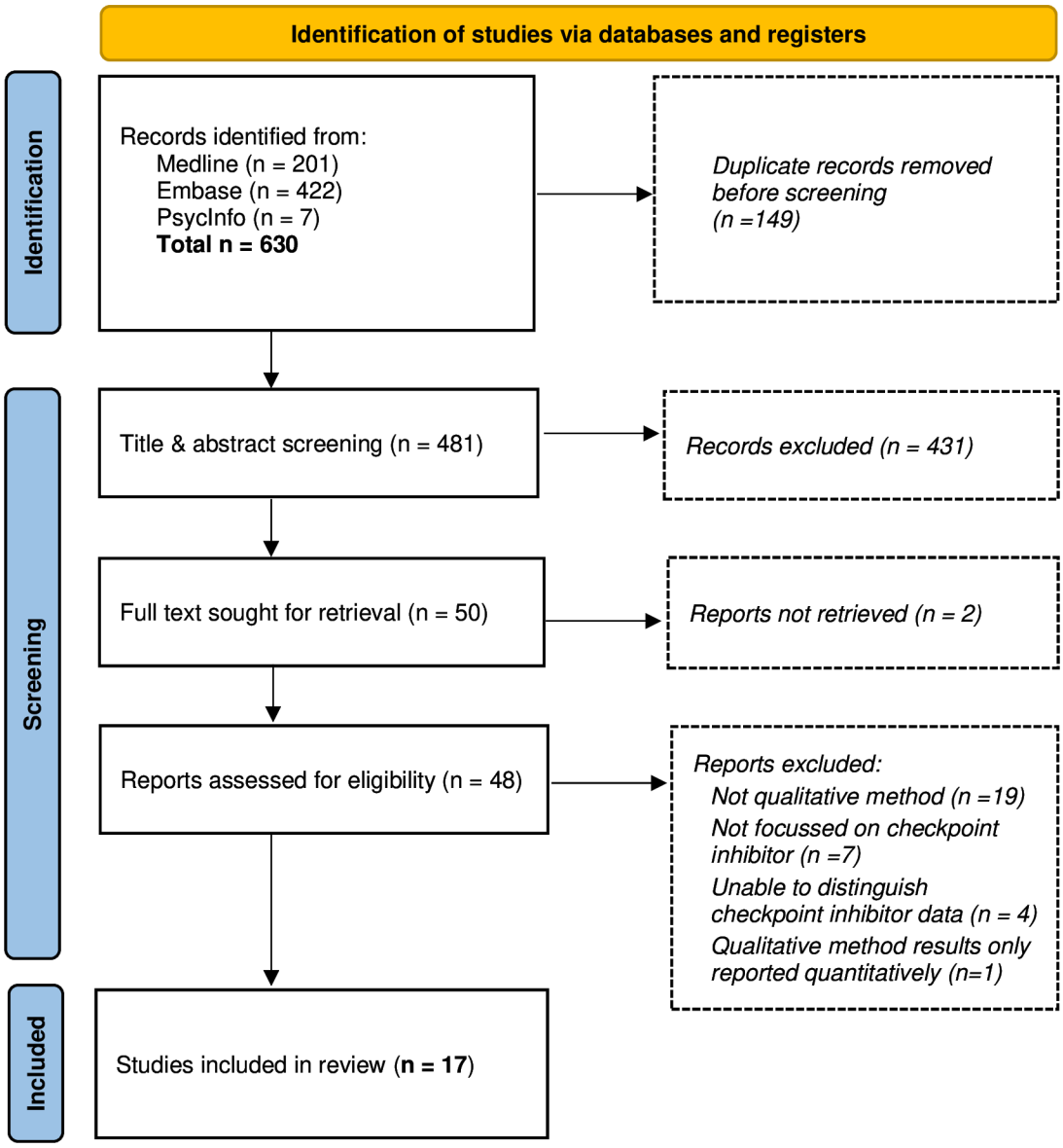

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the process from article identification through ultimate selection for review.

credible findings of qualitative evidence; the checklist does not provide for hierarchical evaluation of quality across all papers.[29]

Data synthesis

All selected papers were uploaded to the NVivo qualitative data analysis software program (QSR International Pty Ltd., V.12, 2018). Consistent with qualitative methodologies used in included studies, thematic analysis and synthesis of qualitative data collected from these studies generated central topics. RY and KL (an experienced qualitative researcher) independently reviewed four of the 17 eligible papers, and by a consensus process established a set of thematic codes. RY applied these to the remaining eleven papers, further developing the codes. A final set of codes was agreed on by reviewer consensus (RY and KL).

RESULTS

Figure 1 shows the results from screening. Overall, a total of 17 studies were eligible. No additional studies were found from reference lists of the 17 identified studies.

Study characteristics

Study characteristics are summarized in table 1. The earliest study exploring patient experience with checkpoint inhibitors was published in 2017, with three papers each from 2018 and 2019, six in 2020, three in 2021, and one in 2022. Of the seventeen selected papers, five (29%) are from Australia and six (35%) from international collaborations. Three papers are associated with the international JAVELIN Merkel 200 trial using Avelumab for Merkel cell carcinoma and were classified by consensus of the research team as separate studies. Both Bharmal *et al*[30 31] papers are from part A of the trial, for patients

Table 1 Summary of included studies

Publication	Year	Country	Participant age (years)	Participant gender (M/F)	Cancer type	Stage	Checkpoint inhibitor	Perspective reported	Study design and methodology
Ala-Leppilampi *et al*[33]	2020	Canada	Median 60; range: 24–85 (of 14 in FGs+23 in interviews)	13:24 (of 14 in FGs+23 in interviews)	Multiple	Advanced	Unspecified	Patient	Cross-sectional, qualitative
Bharmal *et al*[30]	2018	USA, Germany	Mean 70.8 (of nine interviewed)	7:2 (of nine interviewed)	Merkel cell carcinoma	Stage IV	Avelumab	Patient	Longitudinal, mixed methods
Bharmal *et al*[31]	2018	USA. Germany	Mean 70.8 (of nine interviewed)	7:2 (of nine interviewed)	Merkel cell carcinoma	Stage IV	Avelumab	Patient	Longitudinal, mixed methods
Cheung *et al*[40]	2018	Canada	Mean 52; range: 28–69 (of 29 in full study)	11:18 (of 29 in full study)	Melanoma	Advanced	Ipilimumab; pembrolizumab	Patient	Cross-sectional, qualitative
Hyatt *et al*[34]	2019	Australia	Mean 52; range: 34–78	20:34 (one missing)	Melanoma	Advanced, unresectable	Ipilimumab; nivolumab; pembrolizumab	Patient	Cross-sectional, mixed methods
Ihrig *et al*[20]	2020	Germany	Mean 61.5; range: 40–83	4:8	Melanoma, head and neck	Advanced	Nivolumab; pembrolizumab	Patient	Cross-sectional, mixed methods
Jamieson *et al*[35]	2020	UK	Mean 66; range: 48–81 (of 13 interviewed)	10:3 (of 13 interviewed)	Multiple	Unspecified	Atezolizumab; nivolumab; pembrolizumab	Patient	Cross-sectional, mixed methods
Lambert *et al*[32]	2020	USA, Europe, Australia	Mean 70.4 (of 19 interviewed)	16:3 (of 19 interviewed)	Merkel cell carcinoma	Stage IV	Avelumab	Patient	Longitudinal, mixed methods
Levy *et al*[41]	2019	Australia	Mean NS; range: 41–84	16:12	Melanoma	Stage IV	Pembrolizumab	Patient	Cross-sectional, qualitative
Livingstone *et al*[39]	2021	Australia	Patients: median 65; range: 36–82 (of 14 in FGs+10 interviews) Partners: median 69; range: 39–78	Patients: 17:7 (of 14 in FGs+10 interviews) Partners: 4:8	Melanoma	Stage III resected	Nivolumab; pembrolizumab	Patient+partners of patients	Cross-sectional, qualitative
Martin *et al*[36]	2022	USA, Europe	Mean 61.6; range 39–88	36:30	NSCLC	Stage IV	Unspecified	Patient	Cross-sectional, qualitative

Continued

Table 1 Continued

Publication	Year	Country	Participant age (years)	Participant gender (M/F)	Cancer type	Stage	Checkpoint inhibitor	Perspective reported	Study design and methodology
Mieras *et al*[44]	2021	Netherlands	Interviews: NS	Interviews: NS	NSCLC, SCLC	Stage IV	Unspecified	Patient	Cross-sectional, mixed methods
Milne *et al*[16]	2020	Australia	Patients: mean 59; range: 32–86 Carers: mean 49; range: 32–65	Patients: 18:5 Carers: 1:8	Melanoma	Stage IV	Ipilimumab; nivolumab; pembrolizumab	Patient+patient caregivers	Cross-sectional, qualitative
Park *et al*[42]	2020	Denmark, USA, and UK	Denmark (8%); range: 31–50 USA (63%); range: 51–70, UK (29%); range: 71–90	13:11	NSCLC	Stage IV	Atezolizumab; durvalumab; nivolumab; pembrolizumab	Patient*	Cross-sectional, qualitative
Shuk *et al*[43]	2017	USA	Median 63; range: 21–89	28:13	Melanoma	Advanced, unresectable	Ipilimumab	Patient	Cross-sectional, mixed methods
Wong *et al*[38]	2019	Australia	Patients: mean 68; range: 34–92 Carers: NS	Patients: 20:3 Carers: NS	Melanoma	Stage IV	Pembrolizumab	Patient+patient caregivers	Cross-sectional, qualitative
Wong *et al*[37]	2022	USA	All 65+. Of 20 in mixed methods, including 7 not on immunotherapy, 15% 65–69, 45% 70–74, % 75–79 and 26% 80+	Of 20, including 7 not on immunotherapy, 13 (65%) female	NSCLC	Stage IV	Unspecified	Patient	Longitudinal, mixed methods

*Also states that they "recruited" representatives of the patient's "social ecology," which could include family or friends. The points of view of these parties in relation to the patient's experiences were never explicitly reported on. Possible that these participants were incidentally observed in the ethnographic component of the study.
FGs, focus groups; NS, not specified; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

who had failed on chemotherapy, or relapsed after; each used the same qualitative data, with some differences in focus, but use different quantitative data for their mixed-methods analyses. Lambert *et al*[32] is from part B of the same trial for a patient group receiving first-line immunotherapy.

Seven papers evaluated patient experience with checkpoint inhibitors studied patients with advanced stage melanoma, while five studied patients with lung cancer. The most frequently studied checkpoint inhibitors were ipilimumab (four studies, 27%; a CTLA-4 inhibitor) and pembrolizumab (eight studies, 53%; a programmed cell death protein 1 inhibitor). Five studies included treatment regimens that combined concurrent non-immune agents with checkpoint inhibitors.[33–37]

All studies included patients: where known, the patient sample sizes for the qualitative component of the included studies ranged from 9[30 31] to 66.[36] Three studies simultaneously examined the views of carers: one study interviewed an unstated number of carers[38]; the other two studies interviewed 9–12 carers.[16 39]

All studies interviewed some patients on or soon after treatment with a checkpoint inhibitor. Of the 17 studies, none considered the experiences of patients with cancer ineligible for (insurer-subsidized) immune checkpoint inhibitors. Nine studies retrospectively asked patients about their experiences before commencing treatment[20 30 31 35 37 38 40–42] and two studies interviewed melanoma patients before they commenced treatment, one focusing on expectations of those who had decided on treatment[43] and the other focusing on the treatment decision, including patients who declined to commence.[39] Most studies made no mention of the experiences of patients with poor outcomes (eg, no treatment response or who ceased treatment due to side effects) with cross-sectional studies not sampling these populations and longitudinal studies ending with treatment cessation; one notable exception specifically sampled patients with progression, but even this study specifically excluded patients with severe toxicities.[43]

The qualitative components of thirteen studies were based on cross-sectional samples while in the other four studies, patients were interviewed more than once, at different times in the treatment course. All but one study used semi-structured patient interviews; the exception thematically analyzed responses to five open-ended survey questions.[34] Three studies with interviews also had additional components: two used focus groups[33 39]; and one additionally used ethnography.[42]

Qualitative data were obtained as part of a mixed methods study in nine papers. Three studies, one purely qualitative,[40] and two mixed-methods studies,[37 44] explored patient experience on immune checkpoint inhibitors, chemotherapies, and targeted therapies; in these studies, it was only possible to use the subset of data explicitly identified as relating to experience on immune checkpoint inhibitor therapy. As a consequence of these differences, the extent of the extractable qualitative research results was very variable. For example, one study explicitly added some qualitative interviews to elucidate findings in what commenced as an exclusively quantitative study of patients using multiple types of therapy and explicitly reported only one experience clearly attributable to a patient using an immune checkpoint inhibitor.[44]

By contrast, several studies reported detailed data on patient experiences, permitting deeply nuanced interpretations. For example, one study[43] systematically sampled patients before treatment, during treatment, after successful treatment, and after treatment failed to prevent disease progression, thematically exploring the experiences of each group. Another,[42] in addition to interviewing 24 patients, observed each participant for 2 days, both in their homes and as they visited health services.

Quality

Assessment of study quality using the JBI tool is presented in table 2. All 17 papers met four of the 10 dimensions including: congruity between the research methodology and the research question (Q2); the methods used to collect data (Q3); the representation and analysis of data (Q4); adequate representation of participants and their voices (Q8).

Reflexive consideration of the researcher's cultural and theoretical perspectives (Q6) and their influence on the research and vice-versa (Q7) were poorly addressed. Only Levy *et al*[41] reported on both these aspects and the implications of this relationship for their studies. Additionally, the philosophical perspective (Q1) of the papers were seldom identified, so concordance between philosophy and methodology could not be assessed.

Congruity between methodology and interpretation of results (Q5), drawing of conclusions directly from the flow of analysis and interpretation of data (Q10) were generally well addressed, with some exceptions. The reporting of ethical issues (Q9) was deemed to be unclear for several publications[30 31 35 36 40 43] largely because the studies stated they had secured ethics approval but provided no evidence of this (eg, ethics approval number).

Themes of patient experience

Themes identified through reviewer synthesis of the 17 studies are summarized in table 3, grouped within four overarching domains: (1) treatment decision-making; (2) success of immunotherapy; (3) treatment-related AEs; (4) QoL on immunotherapy. Fifteen papers identified themes of patient experience relevant to more than one domain. Domains and supporting example quotes from studies can be found in online supplemental appendix C.

Treatment decision-making

Nine papers identified themes relating to factors of decision-making for patients with cancer considering checkpoint inhibitor therapy. Six of these papers[20 32 33 36 38 43] identified that the option of treatment with immunotherapy provided hope to patients, encouraging them to commence treatment. Three papers noted

Table 2 Johanna Briggs Institute quality appraisal

Quality dimension / Publication	Ala-Leppilampi *et al*[33]	Bharmal *et al*[30]	Bharmal *et al*[31]	Cheung *et al*[40]	Hyatt *et al*[34]	Ihrig *et al*[20]	Jamieson *et al*[35]	Lambert *et al*[32]	Levy *et al*[41]	Livingstone *et al*[39]	Martin *et al*[36]	Mieras *et al*[44]	Milne *et al*[16]	Park *et al*[42]	Shuk *et al*[43]	Wong *et al*[38]	Wong *et al*[37]
1. Is there congruity between the stated philosophical perspective and the research methodology?	Y	N	N	Y	N	N	N	N	N	Y	Y	N	Y	Y	N	N	N
2. Is there congruity between the research methodology and the research question or objective?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Is there congruity between the research methodology and the methods used to collect data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Is there congruity between the research methodology and the representation and analysis of data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Is there congruity between the research methodology and the interpretation of results?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Unclear
6. Is there a statement locating the researcher culturally or theoretically?	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N
7. Is the influence of the researcher on the research, and vice-versa, addressed?	Y	N	N	N	N	N	N	N	Y	Unclear	N	N	N	N	N	N	N

Continued

Table 2 Continued

Quality dimension / Publication	Ala-Leppilampi et al[33]	Bharmal et al[30]	Bharmal et al[31]	Cheung et al[40]	Hyatt et al[34]	Ihrig et al[20]	Jamieson et al[35]	Lambert et al[32]	Levy et al[41]	Livingstone et al[39]	Martin et al[36]	Mieras et al[44]	Milne et al[16]	Park et al[42]	Shuk et al[43]	Wong et al[38]	Wong et al[37]
8. Are participants and their voices adequately represented?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Is the research ethical according to current criteria and is there evidence of ethical approval?	Y	Unclear	Unclear	Unclear	Y	Y	Y	Unclear	Y	Y	Unclear	Y	Y	Y	Unclear	Y	Y
10. Do the conclusions drawn in the research report flow from analysis or interpretation of the data?	Y	Unclear	Unclear	Y	Y	Y	Y	Unclear	Y	Y	Y	Y	Y	Y	Y	Y	Y

that patients trust in the expertise of their clinicians and rely on their recommendations,[20 33 43] while two papers revealed that patients also seek advice from communities of patients with past experiences with immunotherapy.[33 42] Three studies published in the period 2017–2020 found there is limited patient-knowledge of checkpoint inhibitors, potentially contributing to patient apprehension at the prospect of commencing this therapy.[20 41 43]

Success with immunotherapy

The prevailing view of patients across all studies is that checkpoint inhibitors have been a successful therapy. Two studies found patients had a more positive experience with immunotherapy compared with other anti-cancer treatments like chemotherapy or radiation therapy,[32 43] largely attributed to improved tumor response after previous treatment failures. One study found that tumor responsiveness was often concordantly perceived as subjective improvement by patients.[31] Other patient-reported benefits of checkpoint inhibitors include a more manageable treatment regimen,[30 43] better control of cancer symptoms,[40] and improved physical functioning.[35] Despite this, four papers identified that patients also hold a sense of uncertainty about the efficacy of checkpoint inhibitors and whether treatment success would be sustained long-term.[16 41–43]

Treatment-related AEs

Twelve papers identified adverse effects as one of their key themes of patient experience with checkpoint inhibitor therapy for cancer. Fatigue was a common side effect noted among several papers,[16 30 31 33 34 37 40] with some also noting its impact on limiting patient self-care and physical function.[16 30 31 37] Patients in eight studies reported fewer or more manageable treatment-related side effects than their previous therapies.[20 30 31 33 35 38 40 43] Others, however, highlighted the heterogeneity of patient experience and the issue of perception of adverse effects,[33 35] noting that patients are not always able to recognize immunotherapy-related AEs.[35 37 38]

QoL and living with immunotherapy

Overall, the studies found that patients who experienced treatment success with immunotherapy reported better QoL than with previous cancer treatments.[32 41 43] Several studies commented on the impact of treatment-related fatigue on physical function,[30 33 34 37 42] with two of these studies identifying a need for some patients undergoing treatment, to adapt their way of living as a result.[33 42] Apart from physical impacts, some studies noted that persisting uncertainty of immunotherapy response durability can leave patients in a state of "limbo"[42] and anxiety[35]; others highlighted the impact of immunotherapy-specific cost of treatment on patients and the emotional burden of responsibility that falls on caregivers.[16]

Family/caregiver perspective in relation to four identified domains

Three studies invited family members or carers to participate in qualitative investigations. One study only reported

Table 3 Themes identified by included studies

Publication	Treatment decision-making	Success of immunotherapy	Treatment-related adverse events	Quality of life on immunotherapy
Ala-Leppilampi *et al*[33]	Hope Feeling support Faith in medical innovation		Impact Heterogeneity Reframing meaning	Acceptance/adaptation
Bharmal *et al*[30]			Impact on physical functioning	Physical functioning
Bharmal *et al*[31]			Energy/fatigue Pain	Physical functioning
Cheung *et al*[40]			AEs compared with chemotherapy	
Hyatt *et al*[34]			Impact on exercise	Ability to exercise
Ihrig *et al*[20]	Hope Trust in medical expertise		AEs are manageable	
Jamieson *et al*[35]	Treatment considerations		Reporting and managing AEs Heterogeneity	Cyclical anxiety
Lambert *et al*[32]	Hope Anticipation of starting treatment	Success of ICIs compared with chemotherapy		Physical/psychological/social well-being on ICIs
Levy *et al*[41]	Uncertainty of decision-making	Uncertainty about novelty/success of ICIs		Uncertainty impacting family relationships
Livingstone *et al*[39]	Information seeking Perceived risks vs benefits Healthcare team relationships Treatment consideration			
Martin *et al*[36]	Hope Perceived risks vs benefits		Reporting/not reporting AEs Views of AEs vs treatment benefits	
Mieras *et al*[44]		Treatment goals		
Milne *et al*[16]		Uncertainty of treatment response/success	Confusion around AEs Fatigue	Financial toxicity Carer responsibility
Park *et al*[42]	Community support	Uncertainty of treatment response/success		Renegotiation of life
Shuk *et al*[43]	Hope/cautious optimism Uncertainty of decision-making Trust in medical expertise	Comfort with treatment timeline Symptom relief Uncertainty of treatment failure ICIs compared with previous therapies	Limited AEs	Limited impacts of ICIs on QoL
Wong *et al*[38]	Hope Clinician recommendation Health literacy/ICI knowledge		Perception of AEs	
Wong *et al*[37]			Fatigue	Functional change

AEs, adverse events; HRQoL, health-related quality of life; ICIs, immune checkpoint inhibitors; QoL, quality of life.

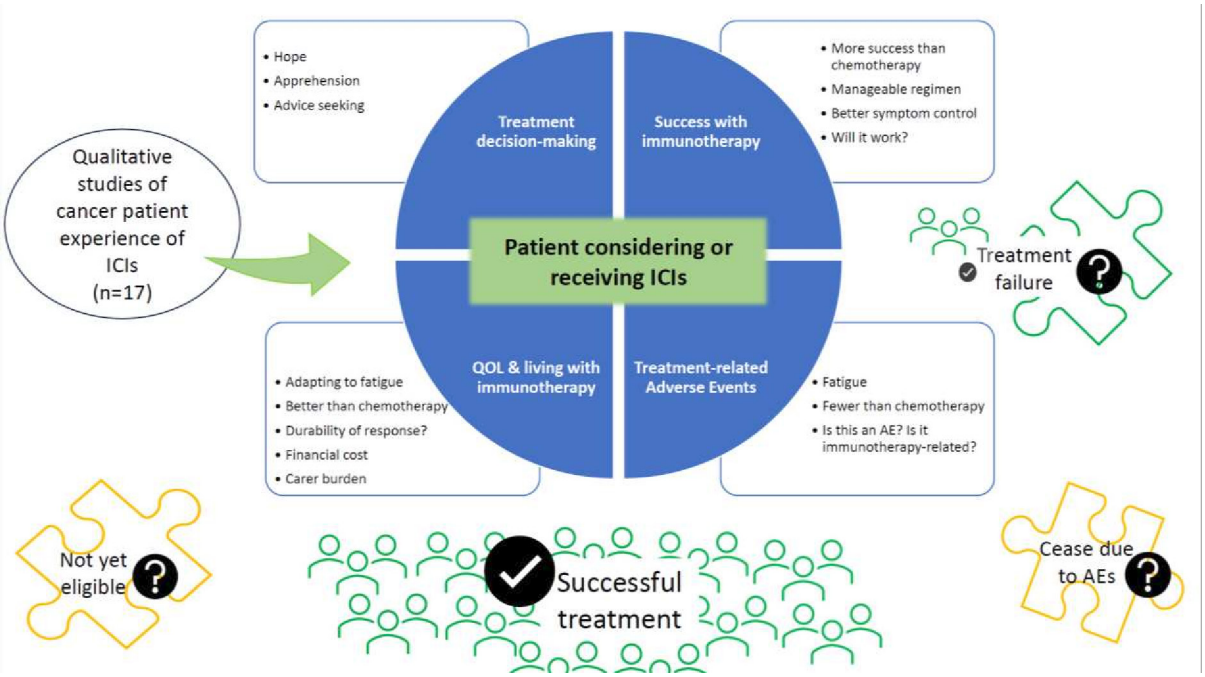

Figure 2 This systematic review of qualitative studies yielded 17 included papers. Patient experience of checkpoint inhibitors could be summarized into four domains: treatment decision-making; success with immunotherapy; treatment-related adverse events; and quality of life and living with immunotherapy. The studies overwhelmingly focus on patients who experienced successful treatment; questions therefore remain with regards to the experiences and needs of ineligible patients, patients without treatment response and patients who ceased treatment due to AEs. AEs, adverse events; ICIs, immune checkpoint inhibitors; QoL, quality of life.

on one carer experience.[38] The other two contrasted patient and carer experience. Livingstone *et al*[39] found carer experience echoed that of patients; viewing immunotherapy as a hopeful opportunity to prolong survival for their loved ones and noting that there is a need for informational support from trusted medical experts. Milne *et al*[16] contrasted patient and carer perspectives, highlighting the special responsibility of caregivers in identifying and helping manage toxicities, as well as their role in pragmatic planning for the future.

DISCUSSION

To our knowledge this is the first systematic review consolidating published qualitative research evidence on patient experience of checkpoint inhibitors in the treatment of cancer; a graphical abstract summarizing our approach and findings can be found in figure 2. The studies included in this review met most criteria for formal assessment of qualitative research quality, but rarely discussed the relationship between researcher and patient, which is a key methodological issue in qualitative research. To improve quality and rigor, future qualitative researchers investigating immunotherapy experience should be explicit about their reflexive considerations of the impact that individual researchers may have on a study and the potential for participant misconceptions.[45 46] Aside from the formal assessment of quality, we note a widely variable qualitative research focus, with over half the studies using mixed methods, with some studies contributing relatively little data to our review.

Our review found that the relative novelty of immunotherapy as a modality for treating cancer results in limited knowledge about checkpoint inhibitors prior to treatment commencement.[20 35 42] As a result, patients may be apprehensive or anxious at the prospect of starting this treatment.[41 43] In line with findings for other cancer therapies,[47–49] our review showed that the decision to proceed with immunotherapy is strongly influenced by clinician recommendation,[20 38 39 43] underpinned by a positive patient–practitioner relationship.[50] As checkpoint inhibitors become available for additional tumor types, care systems can support clinicians in delivering targeted information to promote decision-making by using research that identifies what information patients seek across their cancer journeys.[51]

Our review also found that patients considering checkpoint inhibitors look to community groups to garner advice from patients who have had previous experience with this therapy.[33 42] Support from other patients with similar shared experiences has been shown to mitigate concerns about cancer treatments,[52 53] and may also facilitate new patients' participation in shared decision-making.[47 48] This suggests potential benefits from supportive care processes that routinely link patients who are considering immunotherapy to experienced peers. As checkpoint inhibitors for cancer become more widely used, it is plausible that patient awareness and

understanding of this form of immunotherapy has also grown; other factors, such as concerns about toxicity and efficacy, maybe more significant drivers of patient apprehension in the future.

Immunotherapy as a symbol of newfound hope for patients was a prominent theme across several studies in this review.[16 20 32 33 37 38 42–44] Hope has been shown to improve symptom burden, alleviate psychological distress, enhance QoL[54 55] and act as a key driver to accepting further treatment among this population, even if the optimism is cautious.[56] However, some patients' optimism was tempered by uncertainty over treatment efficacy and durability,[16 32 41–43] following previous treatment failures. Care systems should consider mechanisms to identify this anxiety and provide cancer patients with reassurance support in addition to relevant evidence-based treatment information. However, the expectations of cancer therapy by patients may not always be feasible. Specifically in relation to immunotherapy, it has been noted that clinicians must carefully temper unrealistic patient expectation, without destroying hope.[57]

A notable advantage with immunotherapy reported by patients in our review is fewer or milder adverse effects compared with chemotherapy or radiation,[20 30 31 33 35 40 42] consistent with findings in the literature.[58–60] Nevertheless, the AEs associated with checkpoint inhibitor therapies encompass a vast spectrum of symptoms and severities,[4 61 62] potentially explaining why some patients and caregivers in studies found difficulty identifying their symptoms as adverse or attributing symptoms to immunotherapy.[16 30 35 42] Consequently, patients may under-report AEs associated with immunotherapy because they are uncertain if the sign is due to the disease, a relatively benign consequence of treatment or truly a negative treatment side-effect. Combining checkpoint inhibitors with other treatment modalities is increasingly popular, to maximize the treatment benefit of immunotherapy,[63–65] and it is therefore difficult to delineate the AEs attributable to individual agents. Prompt reporting of patient experience may assist patients and carers to recognize and respond to treatment-related AEs more rapidly.[66] Improved patient reporting of immunotherapy-associated AEs may also facilitate clinicians' knowledge and mitigate under-reporting by practitioners.[8 9]

Treatment-related AEs are inherently linked to a patient's QoL.[67] Fatigue has previously been documented to be a common AE of immunotherapy that is disruptive to QoL and is often the most difficult symptom to manage.[68–70] Studies from our review reinforced these findings.[16 30 31 33 34 37 40] The debilitating impact of fatigue can extend beyond physical functioning and impair a patient's capacity for self-care and their ability to work or participate in activities that previously provided joy and comfort.[71–73] Such factors should be taken into account by clinicians when considering a patient's suitability for checkpoint inhibitors and supportive care interventions need to be routinely available to help the patient cope with fatigue and preserve QoL.

With the exception of fatigue, our review suggests most patients experience their physical function to be unchanged or improved on immunotherapy.[20 30–32 35 43] In some cases, patients even returned to a pre-cancer activity level of functionality while on immunotherapy.[16] While our review did not identify any evidence that checkpoint inhibitors impacted mental health, a recent study reported that patients with multi-line treatment failure are susceptible to anxiety and depression during immunotherapy because of emotional vulnerability due to stressors such as long-term suffering, high financial burden, and low self-healing expectations.[74] Future qualitative studies of immunotherapy should examine the impact of receiving immunotherapy both on physical function and mental health, as important components of patient QoL.

Immunotherapy success and exceeding survivorship expectations was a mixed blessing for some patients in the reviewed studies. These patients found that they had to re-negotiate life decisions they had previously reconciled, such as financial or retirement decisions and even personal relationships.[42] Other patients who had an improved health status on immunotherapy felt undeserving of healthcare supports because they felt fortunate compared with peers without treatment response and did not access the full range of services available to them,[42] supporting findings in the literature on barriers to patients seeking medical care.[75] Support systems should reassure patients about these feeling and ensure they access available services to facilitate optimal QoL.

Caregiver involvement in patients' experiences of cancer treatment is understood to be a fundamental aspect of patient-centered care.[18 19] Our review found limited evidence examining carer perspectives on patient experience. Families and carers share many of the same experiences as their patient counterparts; participating in treatment decisions, finding hope in immunotherapy but uncertain of its longevity, and dealing with patient AE symptoms.[16 39] In addition, family members can also experience stress, anxiety, and fatigue related to their burden of responsibility as caregivers,[16 39] inevitably affecting their ability to undertake their roles of support. Organizational constraints and lack of resources have been reported as factors that limit caregiver engagement.[76] Clinicians and care systems should make a conscious effort to support carers. Publications such as Milne *et al*[16] have identified the value of encompassing the additional perspective of families and carers, alongside patients' experiences, because patients may for example under-report AEs. Nevertheless, this area remains under-addressed in quality measures of healthcare delivery[17] and should be adopted by future studies to continue promoting the importance of person and family-centered care.

Strengths and limitations

To the best of our knowledge, this is the first systematic review of qualitative studies exploring patient experience of checkpoint inhibitors in the treatment of cancer. Despite the diversity of contexts in the studies we were

able to develop analytical domains that captured key themes in patients' experiences of this emerging cancer therapy.

The majority of included papers were focused on advanced melanoma and lung cancers, representing the majority of cancers targeted with the earliest checkpoint inhibitors.[2] Most studies systematically excluded or failed to discuss the experiences of patients for whom immunotherapy was ineffective or where treatment had to be ceased early due to serious AEs; checkpoint inhibitors are reported to be effective for 15%–60% of patients[77] and 7%–59% of patients on these agents suffer "high-grade" AEs.[78] Our results are thus skewed in favor of positive patient experiences, minimizing the importance of AEs and likely ignoring serious AEs; this recommendation is depicted in the graphical abstract in figure 2.

It should be noted that there were no qualitative studies of patients who were ineligible for checkpoint inhibitors, for example, people who have stage III disease, where only patients with stage IV disease are eligible for insurer-funded care. In addition, relatively few studies explored the initial consideration of treatment with checkpoint inhibitors. Therefore, in addition to encouraging focus on families and carers; further exploration into the experiences of these patient groups, and those with no response to treatment or with serious AEs, is required to enhance healthcare delivery for the full spectrum of patients with cancer.[79 80]

Finally, as our focus was exclusively on patient experience we cannot comment on the barriers and facilitators to providing optimal care in response to these emerging treatments. Anecdotally, we are aware of some hospitals developing immunotherapy-specific multidisciplinary meetings, or other support systems such as immunotherapy focused nursing care coordinators. Further research is required to outline these responses and provide setting-specific guidance to system response, such as where additional time, resources, and training are most beneficial.

CONCLUSION

Patient experience has been established as an important measure of healthcare quality alongside clinical effectiveness and patient safety.[81] There is limited research into the subjective experiences of patients with cancer, beyond standardized measures of health-related outcomes in the peer-reviewed literature. Our consolidation of this qualitative evidence suggests a number of areas for further qualitative exploration and possible intervention by clinicians or support systems to enhance the experience of patients considering or undergoing checkpoint inhibitor therapy.

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