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Capturing Real-World Rare Disease Patient Journeys: Are Current Methodologies Sufficient for Informed Healthcare Decisions?

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ABSTRACT

Rationale: Despite growing emphasis among healthcare decision-makers on patient perspectives and real-world outcomes to inform care and access decisions, understanding of patient journey experiences in rare diseases remains limited due to data collection and evaluation challenges.

Aims and Objectives: This systematic literature review (SLR) assessed study designs, methodologies, and outcomes reported in real-world investigations of rare disease patient journeys.

Methods: Searches in PubMed and Google Scholar targeted English-language publications and congress proceedings from 1 January 2014, to 30 April 2024, including rare disease patients, caregivers, or healthcare providers. Keywords included 'Journey', 'Path', or 'Odyssey'. Two reviewers independently assessed eligibility and abstracted data. Descriptive analyses and quality assessments were conducted.

Results: Thirty-one studies met inclusion criteria, with 296,548 participants spanning over 600 rare diseases. Most studies used prospective observational (61%) and cross-sectional (26%) designs and were conducted in Europe (45%). Interviews (39%) and surveys (29%) were common methodologies. Patients (87%) were the primary research focus, compared to caregivers (32%) or providers (10%). The most studied journey stages were 'Pre-diagnosis/Screening' (97%) and 'Diagnosis' (84%), while 'Disease Awareness' (16%) and 'Treatment Adherence' (6%) were less common. Across 164 outcomes reported, frequent outcomes included 'Healthcare Resource Utilization' (94%), 'Symptoms' (74%), and 'Time-to-Diagnosis' (71%). Fewer studies reported 'Costs' (19%), 'Caregiver/Family Burden' (16%), and 'Productivity' (13%). Time-to-diagnosis averaged 11.8 years and a median of 6.1 years. All but one study (97%) was rated low or very low quality due to observational designs.

Conclusion: Most rare disease patient journey evidence focuses on 'Pre-diagnosis/Screening' and 'Diagnosis' stages using qualitative methods and surveys. While symptoms, time-to-diagnosis, and resource utilization were commonly reported, evidence gaps included treatment adherence, caregiver burden and productivity. Longitudinal assessments to collect real-world care and treatment burden outcomes, including caregiver perspectives, can enhance both clinician and policy decision-making for individuals living with rare diseases.

1 | Introduction

Healthcare policymakers are increasingly prioritizing patient perspectives and real-world outcomes to inform guidelines for care and appropriately direct access to treatments that are safe, effective and cost-effective [1–3]. Within this context, patient journey mapping is an emerging field of research that aims to elucidate patient experiences and interactions with healthcare providers, services and systems throughout the disease continuum [4]. Recent guidance from numerous health technology assessment (HTA) agencies links patient journey factors to improvements in diagnosis timelines and treatment effectiveness [5–7]. This shift reflects a growing recognition that traditional clinical trial data, while valuable, often fails to capture the full spectrum of patient experiences and outcomes in everyday settings [8, 9]. Real-world evidence (RWE) and patient-reported outcomes (PROs) provide critical insights into the effectiveness, safety and quality of life (QOL) impacts of treatments from the patient viewpoint [9, 10] to better inform care decisions.

Understanding the patient journey is particularly crucial in the context of rare diseases, where delays and misdiagnoses are common, treatment options are often non-existent or limited, and access to specialized care can be challenging [11–13]. The role of RWE in access decisions (such as coverage and pricing determination) for rare diseases is expected to continue growing in the coming years [14]. Yet, data on patient experiences can be especially challenging to collect and evaluate for rare conditions given small and fragmented patient populations [15]. The limited number of patients often means that large-scale studies are not feasible, resulting in reliance on smaller, less generalizable datasets [15, 16]. Additionally, the heterogeneity of rare diseases, with varied symptoms and progression patterns, complicates the standardization of data collection methods [17, 18].

Although the importance of elucidating the experiences of rare disease populations to enhance care has been documented [19, 20] and prior studies have synthesized methodologies and outcomes for patient disease journeys in general [21–24]; to date, no studies have examined these factors in the rare-disease patient population. The aim of this study was to systematically evaluate the body of patient journey evidence in rare conditions and relevance to clinical and access policy decision-makers.

2 | Methods

2.1 | Scoping Review

To inform this research, we first conducted a scoping review to assess how the concept of the 'patient journey' is discussed in the literature. Since 'patient journey' is not a controlled vocabulary term in literature databases such as PubMed. Based on this assessment, we prioritized the keywords 'Journey', 'Path', or 'Odyssey', to capture the appropriate breadth of literature on this subject.

2.2 | Systematic Literature Review (SLR)

After completing the scoping process, we designed a SLR protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Full details on the SLR methodology, including search terms, can be found in Supporting Information and the study protocol (PROSPERO CRD42024554395).

We sought to answer the following research questions:

1. What study designs and methodologies have been utilized to assess the real-world rare disease patient journey?
2. Which aspects of the rare disease patient journey are most and least reported in literature?
3. What are the most and least reported outcomes within rare disease patient journey research?

2.3 | Search and Selection Procedures

The SLR search strategy was executed in May 2024 using PubMed and Google Scholar according to study Population, Intervention, Comparator, Outcomes and Study Design (PICOS) criteria (Table 1). Inclusion criteria specified English-language publications and congress proceedings that included rare disease patients, caregivers or healthcare providers published from 1 January 2014, to 30 April 2024.

Given our research focus on real-world patient journey assessments, we prioritized observational studies and open-label research for inclusion, as these are the predominant study designs used to generate real-world data (RWD) [25]. Clinical trials, in addition to secondary reviews, narratives, case studies and animal studies, were excluded. We relied on common frameworks from regulatory bodies to inform our interpretation of RWD, which describe these data as derived from sources other than traditional clinical trials, including claims databases, electronic health records, registries, interviews and mobile health technologies [1, 26].

2.4 | Abstraction and Analysis

Two independent reviewers assessed publication eligibility, with disagreements adjudicated by a third reviewer. Following publication selection, two reviewers abstracted data on publication information, study design and methodology, patient journey elements and outcomes.

Qualitative synthesis was employed to descriptively summarize the final body of literature. An adapted patient journey framework from Devi et al. [27] was utilized to characterize study results, which encompasses five discrete journey stages: (1) Disease Awareness, (2) Pre-diagnosis/Screening, (3) Diagnosis, (4) Treatment and (5) Adherence. The stages are defined as follows:

1. Disease awareness: Health promotion, disease awareness, and patient and provider education.
2. Pre-diagnosis/screening: Disease screening, testing and risk assessment.
3. Diagnosis: Diagnosis made by a healthcare provider, treatment decision, emotional impact of the diagnosis and immediate post-diagnosis support.

TABLE 1 | SLR eligibility criteria.

Acronym	Definition	Inclusion criteria	Exclusion criteria
P	Population	Patients diagnosed with a rare disease Caregivers of patients diagnosed with a rare disease Healthcare providers of rare disease patients	Other populations
I	Intervention	None, any	None
C	Comparator	None, any	None
O	Outcomes	Patient journey-related outcomes (e.g., symptoms, QOL, HRU, costs, caregiver impact, treatment experience)	Non-patient journey outcomes
S	Study design	Retrospective observational studies Prospective observational studies Open label studies Studies must focus on the patient journey and include at least one the following terms: • Journey • Path • Odyssey	Animal studies Case report Case Series Narrative reports SLRs/meta-analyses/other reviews randomized clinical trials
n/a	Publication types	Peer-reviewed publications Congress proceedings (abstract, poster)	Opinion pieces Commentaries Editorials Grey literature
n/a	Publication Date	1 January 2014 to 30 April 2024	Before 1 January 2014
n/a	Language	English	Non-English

4. Treatment: Treatment experience, monitoring and access to care.
5. Adherence: Compliance with therapy, chronic management and impact on QOL.

2.5 | Quality Assessment

Quality and risk of bias assessments were performed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [28].

3 | Results

3.1 | Descriptive Publication Characteristics

Thirty-one publications met eligibility criteria and were included in the final review (Figure 1). Most publications (30, 97%) [29–58] were original research and employed an observational study design (Table 2). Geographically, just under half of the studies were conducted in Europe (14, 45%) [29, 30, 33–35, 37, 44, 45, 47–49, 51, 57, 59], followed by North America (12, 39%) [31, 35, 36, 38–40, 45, 48, 50, 53, 55, 56]. Over 600 rare diseases were investigated across reviewed publications, most of which assessed multi-system diseases (10, 32%) [38, 44, 46, 48, 49, 51, 53, 54, 56, 59], followed by immune system diseases (5, 16%) [36, 39, 41, 47, 55], brain and nervous system diseases (3, 10%) [34, 37, 43] and musculoskeletal system diseases (3, 10%) [29, 30, 35]. Almost a fifth of publications did not specify the disease system (6, 19%) [31–33, 50, 57]. Nearly two-thirds (20, 65%) [29, 30, 34–37, 40–45, 47, 48, 51, 52, 54–56, 59] of studies assessed a single rare disease (Table 2). Among publications that reported a specific disease assessed ($n = 27$) [29, 30, 33–49, 51–56, 58, 59], the most frequently assessed disease was Hereditary Angioedema (3, 11%) [41, 47, 55], followed by Fabry Disease (2, 7%) [49, 54] and Gaucher Disease (2, 7%) [48, 49].

Reviewed publications encompassed 296,548 participants, with most studies querying rare disease patients (27, 87%) [29, 30, 33–45, 47–50, 52–59] versus caregivers (10, 32%) [31, 32, 36–39, 44, 46, 48, 59] or healthcare providers (3, 10%) [43, 48, 59] (Table 2). One study (3%) included all three target populations in their patient journey evaluation [44]. Among studies involving patients, most investigated outcomes among adult participants (age ≥ 18; 21) [30, 33–37, 39–42, 44, 45, 47–49, 53–58], 11 studies assessed pediatric patients [29, 30, 36, 39, 43, 44, 48, 50, 53, 54, 57] and 5 [38, 47, 49, 52, 59] investigated both pediatric and adult populations.

3.2 | Employed Study Methodologies

Varied data collection approaches were utilized across reviewed studies. Interviews were the most common approach (12, 39%) [31, 32, 37, 39–42, 45, 46, 51, 57, 59], followed by surveys (9, 29%) [30, 34, 36, 44, 47–49, 54, 55], and chart reviews (7, 23%) [29, 37, 42, 43, 50, 52, 53] (Figure 2).[1] Four (13%) studies utilized multiple data collection modalities [37, 39, 42, 53], three of which employed a mixed-methods approach, combining interviews with another data collection technique

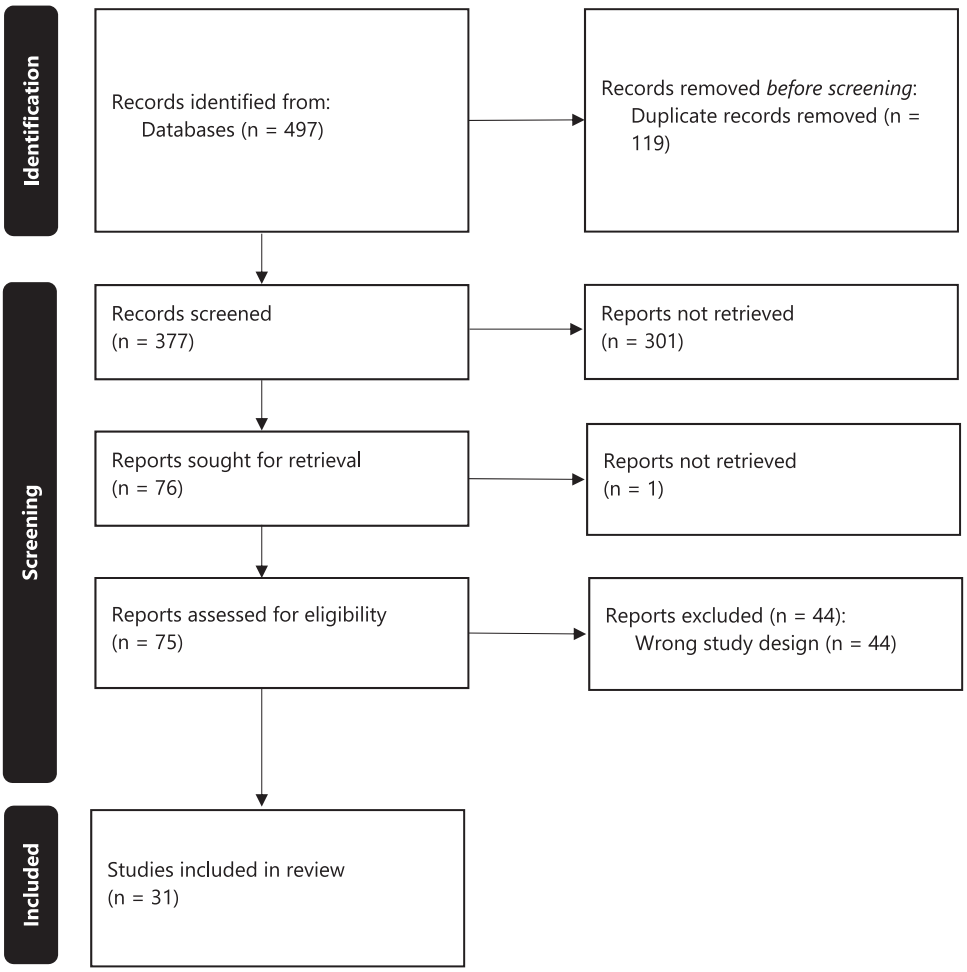

FIGURE 1 | SLR PRISMA flow diagram. PRISMA flow diagram of publication identification in a systematic review of real-world rare disease patient journey assessments.

[37, 39, 42]. Across included studies, the majority of studies used a cross-sectional design (26, 84%) [29–34, 36–44, 46–50, 53–55, 57–59], and 6 (19%) [35, 45, 51–53, 56] conducted a longitudinal assessment. Longitudinal studies ranged in length from 25 weeks [45] to 5 years [56]. The most common data collection method among studies with prospective designs ($n = 21$) [30–32, 34–37, 39–42, 46–49, 51, 53–55, 57, 59] was qualitative interviews (10, 48%) [31, 32, 39–42, 46, 51, 57, 59], whereas quantitative chart review (6, 46%) [29, 37, 43, 50, 52, 53] was the most common approach among studies with retrospective designs ($n = 13$) [29, 33, 37–39, 42–44, 50, 52, 53, 56, 58] (Figure 3).[1] The single open label study reviewed involved qualitative interviews [45].

Of the 12 articles that conducted interviews, 11 (92%) [31, 32, 37, 39–42, 45, 46, 51, 57] were conducted by a facilitator, and one did not specify who conducted the interview [59]. Most interview-based studies were conducted in-person (8, 75%) [31, 32, 37, 40–42, 46, 51], followed by phone (4, 33%) [32, 39, 45, 57], and online (3, 25%) [31, 39, 41], and one (8%) [59] study did not specify interview method. Of these, 4 (33%) [31, 32, 39, 41] utilized more than one modality (online, by phone, or in-person). In all but two (10, 83%) [31, 32, 37, 39–42, 45, 46, 51, 57] interview studies, interviews were administered by a study researcher (one study utilized physician-led medical interviews [37], and one did not specify an administrator) [59]. All but two of the interview studies (10, 83%) [31, 32, 37, 39, 41, 42, 45, 46, 57, 59] were described as semi-structured interviews; the other two (17%) did not specify an interview approach [40, 51].

Among the nine survey-based studies, five (56%) [30, 34, 36, 44, 48] were self-administered, two (22%) [47, 49] conducted by a facilitator, and two (22%) [54, 55] did not specify administration type. Amongst these studies, four (44%) [34, 36, 44, 48] were conducted online, three (33%) [30, 44, 55] in-person and two (22%) [47, 49] over the phone. One survey that was self-administered utilized two modalities, both online and in-person, depending on patient preference [44]. One publication, a patient registry assessment, reported using validated instruments during data collection, including the brief pain inventory (BPI), stiff numerical rating scale (NRS), patient-reported outcome measurement information system physical functioning (PROMIS-PF) and EuroQoL 5D (EQ-5D) [35].

Heterogeneity was observed in methodologies used to assess outcomes across patient journey stages. All five (16%) [41, 44, 48, 51, 57] of the publications that included 'Disease Awareness' in their assessment incorporated PROs. Data collection methods included interviews [41, 51, 57] and expert-reviewed patient surveys [44, 48]. Three studies utilized patient and/or caregiver

TABLE 2 | Baseline study and participant characteristics.

Variable	*n* (%)
Total studies	31 (100)
Minimum sample size, *n* patients	8
Maximum sample size, *n* patients	292,617
Study population[a]	
Patients[b]	27 (87)
Pediatric	11
Adult	21
Age not specified	5
Caregivers/family	10 (32)
Healthcare provider	3 (10)
Publication type	
Original Research	30 (97)
Conference Proceeding	1 (3)
Study location[c]	
Europe	14 (45)
North America	12 (39)
Asia and Pacific	9 (29)
South America	2 (6)
Study design	
Observational	30 (97)
Prospective	19 (61)
Retrospective	11 (35)
Open label	1 (3)
Disease organ systems	
Blood and circulatory	1 (3)
Brain and nervous system	3 (10)
Musculoskeletal	3 (10)
Integumentary	2 (6)
Endocrine	1 (3)
Immune	5 (16)
Multi-system	10 (32)
Not specified	6 (19)
Number of diseases assessed[d]	646

[a]Eight studies reported multiple study populations [36–39, 44, 48, 57, 59].
[b]Ten studies that included patients spanned multiple age demographics [30, 36, 39, 44, 47–49, 53, 54, 57].
[c]Three studies were multi-regional [35, 45, 48].
[d]Four studies did not specify number of diseases assessed [31, 32, 50, 57].

interviews [44, 51, 57], one of which also included physicians' perspectives. [44] Data collection methods for 'Pre-diagnosis/Screening' journey stage investigations ranged from patient and physician surveys [30, 34, 36, 44, 47–49, 54, 55] and interviews [31, 32, 37, 39–42, 45, 46, 51, 57, 59] to medical chart reviews [29, 43, 50, 53], patient registries [33, 35, 38, 58] and claims analyses [53, 56]. Studies assessing the 'Diagnosis' stage employed interviews [31, 32, 37, 39–42, 45, 46, 51, 57], while others used patient surveys [34, 36, 44, 47, 49, 54, 55] and chart reviews [29, 37, 42, 43, 52, 53]. Data collection methods also varied for

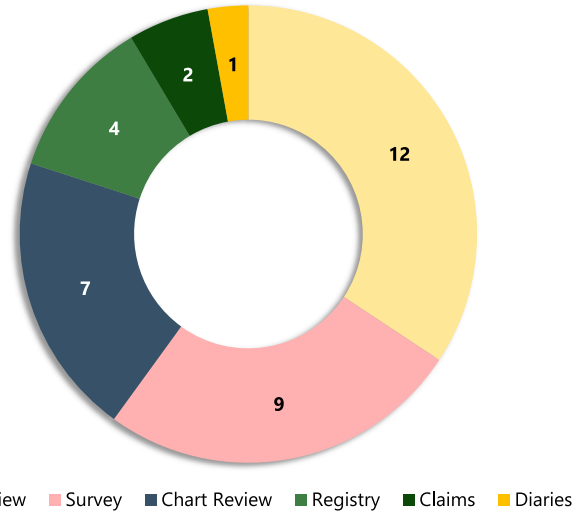

FIGURE 2 | Frequency of data collection methods employed ($n = 31$). Four studies utilized more than one data collection method [37, 39, 42, 53]. Pie chart illustrating the number of SLR publications employing each type of data collection method.

the 'Treatment' stage, including patient surveys [30, 34, 54, 55] and interview-based studies [31, 32, 34, 39, 40, 42, 45, 46, 51, 57, 59]. Two different data collection approaches were used among the 2 'Adherence' stage studies: Vargas-Camaño and colleagues used a cross-sectional survey, and Tada [52] used a longitudinal chart review.

3.3 | Rare Disease Patient Journey Elements

Among the five patient journey stages, the most frequently studied stage was 'Pre-diagnosis/Screening' (30, 97%) [29–51, 53–59], and the least frequently studied was 'Treatment Adherence' (2, 6%) [52, 55] (Figure 4). Of reviewed publications, 3 (10%) [51, 55, 57] assessed 4 different patient journey stages, 14 (45%) [30–32, 34, 35, 39–42, 44–46, 52, 54] assessed 3 stages, 12 (39%) [29, 33, 36–38, 43, 47–49, 53, 58, 59] assessed 2 stages, and 2 (6%) [50, 56] assessed a singular stage, 'Pre-diagnosis/Screening'.

3.4 | Disease Awareness

Patient awareness of rare diseases was found to be limited across the studies reviewed. In Isono and colleagues, one patient was aware of HAE before experiencing symptoms. In this same study, some patients reported adapting to their condition without suspecting a rare disease [41]. Low disease awareness among healthcare providers was also observed, with Mehta and colleagues and Witt and colleagues reporting significant gaps in understanding among healthcare professionals, leading to frustration among patients and family members. Diagnostic delays were often linked to awareness gaps, with calls for better rare disease education among healthcare providers [31, 48]. In pediatric cases, early warning signs were frequently overlooked, as highlighted by Somanadhan and colleagues, where parents and/or caregivers missed symptoms

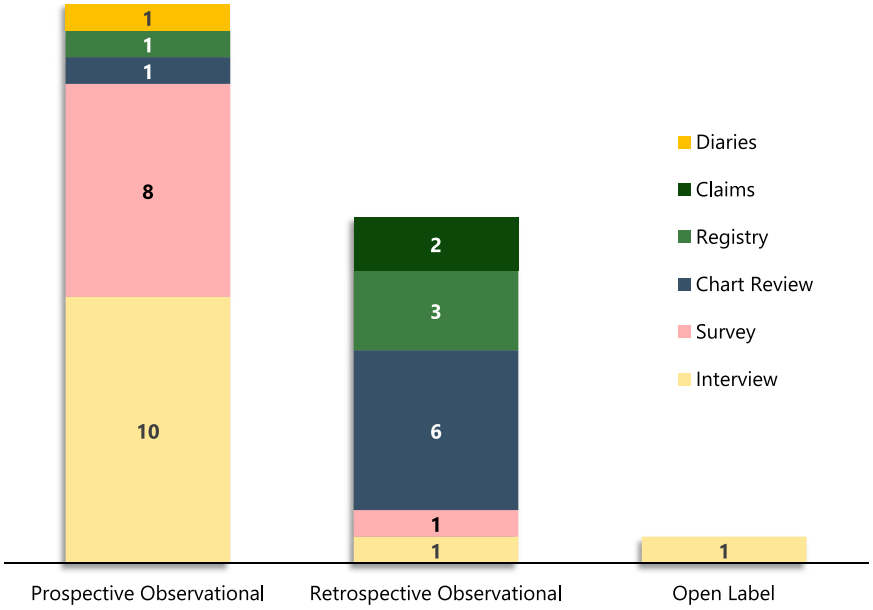

FIGURE 3 | Data collection methodologies by study design ($n = 31$). Four studies utilized more than one data collection method [37, 39, 42, 53]. Bar chart illustrating the number of SLR publications employing each type of data collection method by study design.

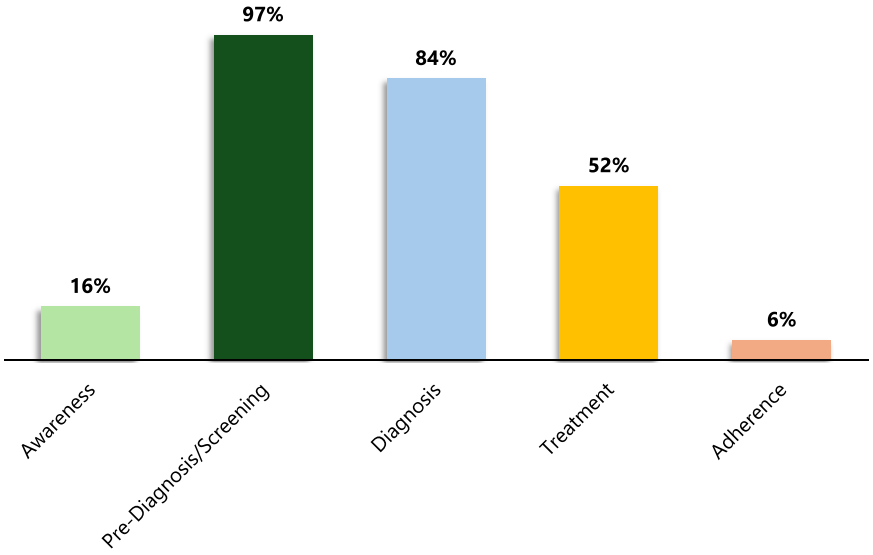

FIGURE 4 | Proportion of publications investigating patient journey elements ($n = 31$). Bar graph illustrating the proportion of SLR publications investigated across the five stages of the patient journey.

due to continued developmental milestones being met. One recurring theme within 'Disease Awareness' stage literature was the responsibility placed on patients and caregivers to seek out information about their child's conditions. Lagler and colleagues found that self-initiated searches were the primary source of information for patients and caregivers, and patients' parents interviewed in Somanadhan and colleagues described this process as difficult and frightening.

3.5 | Pre-Diagnosis/Screening

Lengthy time-to-diagnosis was a hallmark of the 'Pre-diagnosis/Screening' phase. This period was characterized by multiple specialist visits and extensive testing. For instance, Delgado-Garcia and colleagues reported an average time-to-diagnosis of 2.2 years while Mengel and colleagues reported diagnostic delays of up to 21 years for diseases like Fabry and Gaucher, with patients often seeing multiple physicians. Furthermore, studies including Baumbusch and colleagues, Lambert and colleagues, Delgado-Garcia and colleagues, Lagler and colleagues, Mengel and colleagues and Bernthal and colleagues all found that patients visited several specialists and underwent numerous tests before receiving a correct diagnosis. The emotional toll on patients and caregivers related to this diagnostic odyssey was significant, with studies like Benito-Lozano and colleagues, Vargas-Camaño and colleagues, and Muir and colleagues emphasizing the psychological strain associated with prolonged uncertainty. Several studies reported high rates of misdiagnosis among rare disease participants. For instance, in studies from Benson and colleagues, Grier and colleagues and Mengel and

colleagues, over half of respondents experienced at least one misdiagnosis before receiving the correct one. A number of studies reported that geographic location was a determinant of timely and appropriate diagnosis, particularly for patients in areas without specialized facilities or centres [30, 42, 46, 58]. As a result, patients referred to specialized centres lengthy distances from home for assessment often experienced prolonged diagnostic delays [46, 58]. Systemic healthcare issues, such as poor communication, fragmented services, and insurance issues compounded these challenges. For example, parent participants in a study by Somanadhan and colleagues reported that insurance providers frequently required additional testing to confirm their child's diagnosis, prolonging uncertainty [40].

3.6 | Diagnosis

Studies reporting on the 'Diagnosis' journey stage often focused on the range of emotional responses experienced upon receipt of a diagnosis, from initial devastation and anger to eventual relief and validation. Hausmann and colleagues, Isono and colleagues and Lambert and colleagues described parents' feelings of validation and relief upon receiving the accurate diagnosis for their children, despite this often leading to additional concerns and questions. Parents and caregivers also noted feeling isolated and burdened with the responsibility of planning next steps once a diagnosis was provided [31, 32]. Baumbusch and colleagues found that, even after obtaining a diagnosis, parents of rare disease patients expressed frustration with the barriers they faced accessing services. Respondents went on to say that a secondary diagnosis of a disease-related condition was sometimes more helpful in finding a supportive network for their child living with a rare disease. Similarly, while parents of children diagnosed with rare disease stated they found the diagnosis provided context for their child's disease, the diagnosis itself did not change their child's health situation or life trajectory [31].

Disclosing the diagnosis to others posed a separate set of challenges, as patients and families struggled with explaining the condition, justifying absences for medical reasons and addressing misconceptions from others [33, 39]. Meanwhile, taking action to manage the condition involved, navigating a complex healthcare system and accessing necessary treatments and support, often required significant effort and advocacy from patients and caregivers [34, 40]. This process included securing appropriate medical care, coordinating multiple appointments and ensuring continuity of care, which could be particularly burdensome in regions with fewer specialized resources [30, 46, 58].

3.7 | Treatment

The 'Treatment' phase of the rare disease patient journey was found to encompass a range of challenges related to financial and organizational barriers to treatment. For instance, Baldelli and colleagues, reported that 88.24% of patients forwent treatment due to costs and scheduling conflicts. Patient-reported treatment satisfaction varied, with Tsurumi and colleagues reporting that while 48% of Fabry disease patients felt positive about receiving treatment, 23% experienced increased anxiety. Similar variability was observed in Vargas-Camaño and colleagues, where 65% of HAE patients found their treatments effective, often necessitating treatment changes. Many patients across the rare diseases reviewed required supplementary therapies, such as occupational therapy and psychiatric evaluations, due to the emotional and physical toll of their conditions [35, 39, 51, 57]. Somanadhan and colleagues reported a preference for home-based treatments due to patient-perceived benefits in routine and structure. The importance of effective patient education and managing expectations was emphasized across studies in this journey stage [31, 40, 51].

3.8 | Adherence

Amongst both studies assessing treatment 'Adherence', challenges maintaining long-term adherence to treatment were reported. While Tada and colleagues reported high initial treatment adherence, with 97.0% of patients receiving a first-line therapy for generalized pustular psoriasis (GPP), 80% of patients went on to receive a second-line therapy where frequent treatment switching was noted, most commonly among patients treated with biologics, such as infliximab (52.2%) and ustekinumab (71.4%) [52]. Vargas-Camaño and colleagues also reported frequent treatment alterations, with an average of three treatment changes due to issues such as treatment unavailability, administration problems, and side effects. Patients receiving treatment faced significant side effects, with some requiring critical interventions such as frozen fresh plasma (52.9%) and adrenaline (17.6%) for their acute HAE attacks [52]. The study emphasized that the barriers of unavailability and difficult administration, along with the adverse effects experienced by patients, significantly impacted adherence to treatment regimens. Additionally, 41.2% of patients reported needing psychological support, highlighting the emotional toll of managing their condition and the treatments associated with it [55].

4 | Outcomes Reported

A total of 164 outcomes were reported across the 31 publications. The most examined outcome was 'Healthcare Resource Utilization' (HRU) (29, 94%) [29–44, 46–56, 58, 59], followed by 'Symptoms' (23, 74%) [29, 32, 34–49, 51, 54–56, 59] and 'Time-to-Diagnosis' (22, 71%) [29–31, 33, 35–37, 39, 41, 42, 44, 45, 48–51, 54, 55, 57–59] (Figure 5). Comparatively fewer studies explored 'Costs' (6, 19%) [30, 31, 40, 42, 46, 53], Caregiver/Family Burden', (5, 16%) [31, 32, 42, 46, 57] and 'Productivity' (4, 13%) [33, 35, 55, 57] in the context of the patient journey assessment. Almost half (15, 48%) [30, 31, 35, 36, 40–42, 44, 48, 49, 51, 54, 55, 57, 59] of the studies assessed more than five outcomes, and no publications assessed fewer than two outcomes. A mixed-methods study by Kinoshita and colleagues, which conducted semi-structured patient interviews supplemented with medical records, reported the most outcomes (10). Common outcomes among the 9 survey-based studies reviewed included 'QOL' (9, 100%) [30, 34, 36, 44, 47–49, 54, 55], and 'Symptoms' (8, 89%) [34, 36, 44, 47–49, 54, 55]. 'Symptoms'

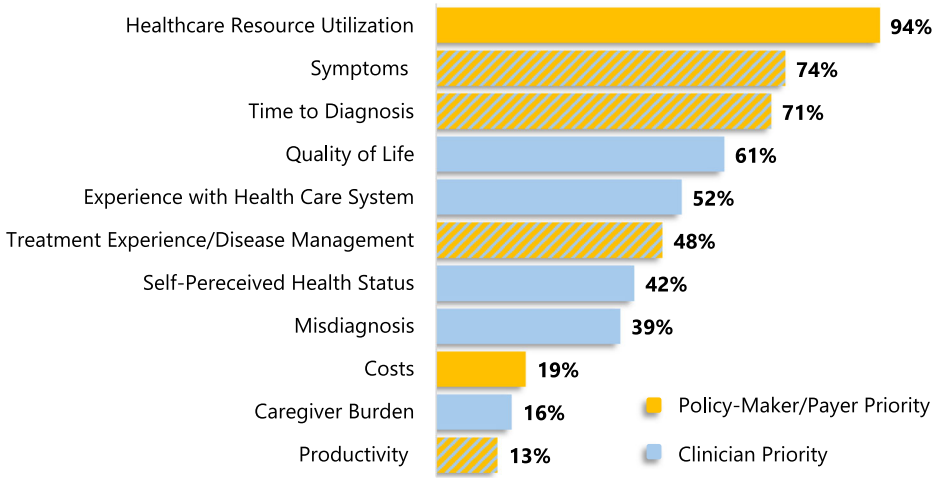

FIGURE 5 | Proportion of publications reporting observed outcomes and their relative importance to healthcare decision-makers ($n = 31$). Bar graph illustrating the proportion of SLR publications examining observed outcomes and their relative importance to healthcare decision-makers.

(10, 83%) [32, 37, 39–42, 45, 46, 51, 59], 'Experience with the Healthcare System' (10, 83%) [31, 32, 37, 39–42, 46, 51, 59] as well as 'QOL' (10, 83%) [31, 39–42, 45, 46, 51, 57, 59] were frequently assessed in the 12 interview-based studies.

Among the three most frequently reported outcomes—'HRU', 'Symptoms', and 'Time-to-Diagnosis'—data collection methods varied. HRU outcomes were reported in all chart reviews (7, 24%) [29, 37, 42, 43, 50, 52, 53], claims analyses (2) [53, 56], and surveys (9) [30, 34, 36, 44, 47–49, 54, 55], as well as in all but 2 interview-based studies [31, 32, 37, 39–42, 46, 51, 59]. While 'Symptoms' outcomes were queried across data collection methods, this outcome was most commonly assessed via interview (10, 43%) [32, 37, 39–42, 45, 46, 51, 59] and least commonly assessed by claims analyses studies (1, 4%) [56]. The 'Time-to-Diagnosis' outcome was most commonly assessed by interview-based studies (9, 41%) [31, 37, 39, 41, 42, 45, 51, 57, 59], least commonly assessed by registries (3, 14%) [33, 35, 58] and not assessed at all by either claims analysis [53, 56].

'HRU' findings consistently highlighted extensive use of resources, including frequent hospital visits and hospitalizations [35, 39, 50, 56], multiple diagnostic tests [38, 45, 55], misdiagnoses [44, 47, 48] and specialist consultations [30, 32, 46, 58]. Reflecting findings in the 'Pre-diagnosis/Screening' patient journey stage, Galvin and colleagues reported a mean of 4.8 tests per patient before diagnosis, while Vargas-Camaño and colleagues found that some patients visited up to 9 medical professionals to ultimately receive their diagnosis.

'Symptoms' outcomes often detailed types of symptoms experienced as well as impacts on patients' interactions with the healthcare system and their overall QOL. For example, fatigue, weakness, anxiety and pain, were all frequently reported symptoms across rare diseases, often resulting in multiple hospital visits and lengthy consultations with specialists [35, 39, 50, 56]. Further extending the patient experience, Delgado-Garcia and colleagues noted that presented symptoms—especially pre-diagnosis—often resulted in the use of generic therapies such as painkillers, which provided only temporary relief and failed to address the underlying disease symptoms comprehensively. These symptoms were also found to have influenced patient well-being and QOL. For instance, symptoms like swelling significantly disrupted daily activities and social participations, placing an emotional burden on patients, which led to increased isolation and stress [33, 51, 55]. Many studies called for not only symptom alleviation but also for better integration of mental health resources intro treatment plans for rare disease patients to provide a more holistic approach to care [33, 57].

'Time-to-Diagnosis' was found to be prolonged, with patients experiencing significant delays that exacerbated their conditions [29, 33, 40, 43, 44, 47, 49]. Across all publications that reported mean ($n = 15$) and/or median ($n = 9$) time-to-diagnosis [29, 30, 35, 37, 39, 41–44, 47, 49, 50, 53, 55, 58], the mean was 11.8 years [30, 37, 41, 43, 47, 50, 53, 55, 58], and the median was 6.1 years [29, 35, 37, 38, 42, 44, 47, 49, 55]. As highlighted in the 'Pre-diagnosis/Screening' section, misdiagnoses further complicated the patient journey, leading to inappropriate treatments and additional psychological strain as seen in Benson and colleagues where stress was blamed for presenting symptoms and Vargas-Camaño and colleagues where incorrect treatment was taken for at least a month up to 30 years across surveyed patients. These diagnostic hurdles not only reported delaying a definitive diagnosis and effective treatment but also contributed to a decline in QOL.

'QOL' was assessed in 19 studies (61%) [30, 31, 33–36, 38, 39, 42, 44, 45, 47–49, 51, 54, 55, 57, 59], highlighting the holistic impact of rare diseases. Studies like Bauskis and colleagues, Witt and colleagues and Somanadhan and colleagues reported significant emotional and psychological burdens on patients and their families across the stages of the patient journey. One study found that parents felt 'unsupported' and 'overwhelmed' by the responsibility of coordinating care for their child [51]. Additionally, while some studies suggested a diagnosis can lead to improved access to resources and support networks, the burden of managing ongoing care was found to remain high [31, 32, 55].

Economic and social impacts were less frequently reported as outcomes among included studies. Costs associated with rare disease management were addressed in 6 studies (19%)

[30, 31, 40, 42, 46, 53], including all data collection types except surveys. Out of these studies, five (83%) [30, 31, 40, 42, 46] assessed direct patient costs, with one (17%) study also reporting on direct health system costs [53]. These studies featured the significant financial burden rare diseases have on patients. For example, Baumbusch and colleagues and Luz and colleagues discussed the substantial out-of-pocket expenses for treatments and therapies, calling on the inadequacy of current government programmes and available insurance coverage. Luz and colleagues went on to report patients resorting to enrolment in experimental trials given their inability to access high-cost treatments. Another study by Tisdale and colleagues noted that rare disease patients on average had costs three-to-fivefold higher than matched controls and are more likely to be underestimated in cost estimates for medical care.

Social impacts, such as productivity, were reported in four studies (13%) [33, 35, 55, 57]. All four studies addressed patient absenteeism from work and/or school due to their condition, and two reported on presenteeism in the workplace [55, 57]. Further, all studies assessed patient productivity, and one also assessed affected productivity of parents/family members due to their kin's rare disease [57]. Specifically, Bernthal and colleagues documented the loss of work hours and changes in employment status, with 56.9% of patients missing work due to symptoms and 11.6% changing employment or retiring early due to the disease burden.

Caregiver and family burden was reported in five studies (16%) [31, 32, 42, 46, 57], all of which were semi-structured interviews. Amongst these studies, four [31, 32, 42, 46] reported practical challenges, including travel time and serving as the care coordinator, expert and advocate for their affected family member. One study evaluated the psychosocial burden on caregivers and family members, revealing that they frequently encountered healthcare professionals who were unempathetic and failed to provide mental health resources or guidance on where to seek further support [57].

4.1 | Quality Assessment

The overall quality of studies in the SLR was found to be acceptable. A GRADE assessment determined that 1 publication (3%) was moderate quality, 23 (74%) were low, and 7 (23%) were very low, reflective of the significant number of observational studies included in the review.

5 | Discussion

While this SLR captured a robust body of recent patient journey research across 600+ rare diseases, heterogeneity was observed in study designs, methodologies and outcomes captured, which may hinder appropriate clinical and access policy decision-making for rare disease populations.

The review identified a diverse array of study designs and methodologies used to capture the rare disease patient journey, with cross-sectional qualitative interviews and surveys being the most common. While these snapshot assessments are useful for illuminating patient experiences, they are inherently static and therefore limit insight into trends and experiences over time. Longitudinal studies are necessary to understand how patient journeys evolve and to identify key factors related to treatment adherence and long-term outcomes; yet, such designs are notably uncommon in rare disease literature, underscoring challenges with long-term follow-up. Previous research in chronic diseases has highlighted value in effectively identifying patterns of disease progression and capturing how patient needs may shift over time [60–62]. Observational registries, often managed by patient societies or academic centres, such as the Rare Diseases Registry Program (RaDaR) and the National Organization for Rare Disorders (NORD), can be valuable sources of data for patient journey assessments, facilitating retrospective and prospective assessment on varied disease, treatment and QOL topics. Leveraging other sources of existing real-world data, such as electronic health records and medical claims, can also provide longitudinal information on patient experiences without the timeline, resource or patient burden constraints of prospective assessments. However, potential data source limitations should be considered when selecting an appropriate real-world data source (e.g., the quality of medical records can vary by context and provider and lack desired outcomes).

Recent health policy, HTA and clinical guidelines have called for increased use of PROs in rare disease to better understand disease and treatment impacts [1, 2, 5, 63], yet our review found that few rare disease patient journey studies are employing such tools. In fact, one study reported utilizing validated patient-reported outcome measures (PROMs) in their assessment [35]. The use of validated instruments in outcomes research ensures the accuracy and reliability of data by providing standardized measurements that can be used in healthcare decision-making [64], including HTA review. Although challenges exist in use of PROMs in rare disease populations, such as variable disease and general lack of disease-specific instruments [19], researchers should consider incorporation of validated PROMs into their patient journey assessments to broaden the applicability of results to key healthcare stakeholders.

Additionally, this review highlighted that limited research to date has focused on the ‘Disease Awareness’ patient journey stage. Disease awareness, including how patients learn about their disease and treatment options, has critical implications for timely receipt of a diagnosis, connection to care and appropriate disease management [65, 66]. Indeed, policy papers and reports from organizations, such as NORD, NHS and United Kingdom Department of Health and Social Care (DHSC), have emphasized the importance of early diagnosis in rare diseases for improving patient outcomes by enabling appropriate management, swifter treatment and linking individuals to vital information and support [2, 6, 67]. There is a particular need for improved education and training among healthcare providers to better identify rare disease signs and symptoms to facilitate appropriate diagnoses. Patient advocacy groups can be an effective conduit through which to coordinate research on journey elements, such as disease awareness, as well as to raise awareness directly amongst policymakers and the public given their connections to patient communities. Although, it is worth noting that their success in these efforts is often dictated by

funding, organizational maturity and the strength of collaborations [68].

We also found the 'Treatment Adherence' journey stage to be infrequently assessed despite its direct implication on patient access and treatment pathways. Prior research has documented the pervasive nature of poor medication adherence among chronic disease populations (e.g., diabetes, hypertension) [69], with linkages to excess mortality and substantial HRU and costs [70]. Yet, the heterogeneity of rare conditions and paucity of available treatments has limited adherence investigations in rare indications, as evidenced by our review. Real-world, direct and indirect treatment assessment approaches have been noted to be ideal for capturing both objective (e.g., measurements of clinical outcomes, dose counts, pharmacy records, electronic monitoring of medication administration) and subjective (e.g., patient assessment of their medication taking behaviour or healthcare provider) treatment adherence insights [71]. Future rare disease assessments should consider such methodologies to probe this important stage of the patient journey, which can inform more patient-centred and responsive clinical and policy decision-making.

Finally, the infrequent reporting of outcomes critical for healthcare decision-makers across reviewed articles, including costs, caregiver/family burden and productivity, highlights a significant gap in the rare disease patient journey evidence base. Payers and market access decision-makers rely on these types of health economics and outcomes research metrics to inform policymaking, resource allocation and the assessment of treatment value. Since collecting this type of data in rare disease can be challenging due to data limitations and methodological complexities, creative and flexible study design approaches that minimize patient and caregiver burden and maximize resources (e.g., digital data collection, real-world data analysis) may be required.

6 | Limitations

While this review offers valuable insights, several limitations should be acknowledged. The heterogeneity of study designs and methodologies presents challenges in drawing uniform conclusions across all rare diseases. Furthermore, our search terms may not have captured all study designs or terminology used to describe the patient experience, for example claims analyses on patient prescription frequency. Our focus on real-world study designs meant clinical trials were excluded. Inclusion of predominantly observational designs, often using secondary sources of data (e.g., medical records, claims) may have introduced bias in the reported results. Additionally, limited data availability for some rare diseases can result in an incomplete understanding of the patient journey. Temporal and regional variations in healthcare systems and practices can hinder the generalizability of findings. Despite these limitations, this review was conducted in accordance with best practice SLR guidelines to minimize bias.

7 | Conclusion

This review underscores the need for more comprehensive patient experience data collection methods to inform patient-centred health policies for rare disease populations. The body of evidence identified predominantly focused on pre-diagnosis/screening and diagnosis patient journey stages queried via cross-sectional qualitative methods and surveys. While patient symptoms, time-to-diagnosis and resource utilization were commonly reported, evidence gaps included treatment adherence, productivity and family/caregiver burden. Additionally, longitudinal studies are needed to provide a more comprehensive view of real-world disease trajectories over time to enhance rare disease clinical and access policy decision-making, and researchers should strive to include diverse rare disease populations to foster a more representative understanding of patient experiences. Lastly, integrating perspectives from both patients and caregivers is necessary to provide a holistic view of the impact of rare diseases on families and support systems.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Endnotes

[1] Four studies utilized more than one data collection method [37, 39, 42, 53].

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.