




ORIGINAL RESEARCH

The Impacts of Caregiving for Patients with X-Linked Retinitis Pigmentosa (XLRP): Findings from the EXPLORE XLRP-2 Study

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ABSTRACT

Introduction: Informal caregivers play an important part in the healthcare of patients with chronic diseases, including those leading to visual impairment. X-linked retinitis pigmentosa (XLRP) is considered one of the most severe forms of retinitis pigmentosa and causes declines in vision starting in childhood, ultimately

progressing to legal blindness in adulthood. Caregivers are expected to play an increasing role in patient care, but real-world impacts of XLRP on caregivers are poorly evaluated.

Methods: EXPLORE XLRP-2 was an exploratory, multicentre, non-interventional study. Cross-sectional surveys were used to gather experiences directly from caregivers across Europe and Israel by both validated and newly developed caregiver-reported outcome surveys.

Results: Seventy caregivers of patients with XLRP associated with retinitis pigmentosa GTPase regulator (*RPGR*) mutations were enrolled, of whom 68 were included in analyses; 87.7% of caregivers were female and mean (standard deviation [SD]) age was 49.4 (11.7) years. They were most commonly either spouses (50.8%) or parents (41.5%) of patients. Caregivers spent a mean (SD) 28.7 (34.5) hours per week caring for patients. Of the 72.3% of caregivers who were employed, 34.8% worked part time; of the 27.7% of caregivers who were

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unemployed, 33.3% cited caregiving responsibilities as a cause for unemployment; 23.1% and 46.2% of caregivers reported any level of depression and anxiety, respectively, with few additional impacts captured by the surveys.

Conclusions: Some caregivers reported employment and mental health impacts in this study. However, despite many hours spent per week caring for patients with XLRP, the surveys did not reflect the expected burden experienced by caregivers, highlighting the need for further research in this field.

Keywords: Caregiver; Burden; Impact; Inherited retinal dystrophy; Real-world; Survey; X-linked retinitis pigmentosa

Key Summary Points

Why carry out this study?

X-linked retinitis pigmentosa (XLRP) is a severe, progressive retinal disease that leads to blindness.

Patients with XLRP face a diverse array of burdens on their everyday lives, yet the wider impact of XLRP on their caregivers is unknown.

What was learned from the study?

Caregivers spent on average nearly 30 hours per week providing care to patients with XLRP, despite the majority of caregivers being employed, and this time tended to be higher for caregivers of patients with severe disease.

Anxiety was higher in caregivers relative to population norms, but we think the true burden on caregivers would be revealed by assessment tools tailored towards this population.

This is the first study to our knowledge to evidence complex disease impacts on caregivers caring for patients with XLRP.

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INTRODUCTION

For many chronic diseases, informal caregivers play a critical role in patient well-being [1]. This role is associated with social, economic and emotional burdens that may be hidden and will vary by disease or condition [1–3]. In particular, diseases that cause visual impairments are known to be burdensome for caregivers, most of whom are spouses of older patients [4–7]. There is little research exploring visual impairments in younger adults or caregivers who are parents of patients.

Retinitis pigmentosa (RP), one of the most common forms of inherited retinal dystrophy, is a family of chronic conditions in which patients experience progressive vision loss, leading in most cases to legal blindness [8]. One of the most severe forms of RP is X-linked retinitis pigmentosa (XLRP), which accounts for 5–16% of all RP cases [9–13] and predominantly affects males, although female patients who are carriers can also experience visual impairments [14–16]. More than 70% of XLRP cases are caused by mutations in the RP GTPase regulator (*RPGR*) gene [10, 12, 17].

Symptoms of XLRP are caused by progressive degeneration of photoreceptors [8]. Patients with XLRP-*RPGR* often first show symptoms in childhood, typically night blindness (nyctalopia) [8]. Vision progressively worsens throughout adulthood, leading to legal blindness, with a median onset age of 26 years based on visual field loss [18] and at 45 years based on visual acuity loss [9]. Therefore, patients with XLRP are expected to require diverse and growing support needs from their caregivers as the disease progresses.

Indeed, providing care for people with chronic conditions associated with visual impairment has significant impacts on the social, economic and overall well-being of caregivers [3], including loss of personal time [4, 5] and elevated emotional distress [6]. In particular, a study of caregivers of patients with RP in Japan found they experienced negative impacts on employment, income and overall quality of life relative to age- and sex-matched general populations [19]. Given the severity of

XLRP, its progressive nature and the lifetime of impact experienced by patients, we might expect the burden placed on caregivers to be greater than that for other forms of progressive vision loss.

The EXPLORE XLRP-2 study was carried out to understand the real-world burden of XLRP on both patients and caregivers. In a separate manuscript [20], we described the impact of XLRP on patients included in this study and found that they faced significant and complex burdens (including impacts on mobility, daily activities, emotional and social life, and finances) that tend to be more prominent at the most severe disease stage [20]. In this article, we focus on understanding the impacts of XLRP on caregivers using a variety of validated and bespoke surveys to reveal the multifaceted societal burden of XLRP.

METHODS

EXPLORE XLRP-2 was a non-interventional study, combining retrospective chart reviews and cross-sectional patient (age ≥ 12 years, with XLRP associated with *RPGR* variant) and caregiver interviews, conducted in 23 centres in 10 countries. Study methods, patient recruitment and data sources have been reported previously [20].

The study received local ethical committee approval at each study site (Austria, Ethik Kommission Medizinische Universität Wien: 1088/2022; Belgium, Ethics Committee Research UZ/UK Leuven: B3222022000832; UK, Health Research Authority Integrated Research Application System: 307690; Finland, HUSin Alueellinen Lääketieteellinen Tutkimuseettinen Toimikunta: 48/2022; France, Comité de Protection des Personnes Nord Ouest IV: 22.02349.000114; Germany, EC Medical Faculty of Eberhard-Karls-University and University Clinic Tübingen: 839/2021BO1, 2022-200343-BO-bet; Israel, EC of the Chaim Cheba Medical Centre: 9186-22-SMC; Israel, EC of the Soroka Medical Center: 0391-21-SOR; Italy, Comitato Ethico di Area Vasta Emilia Centro: 1026/2021/Oss/AOUFe;

The Netherlands, Dutch Clinical Research Foundation: 21.177/VS; Spain, Comité de Ética de la Investigación con medicamentos Euskadi: PI2022051) (see Supplementary Table S2 for more details) and adhered to the tenets of the Declaration of Helsinki. All participants gave informed consent.

Caregivers at each participating site were required to meet these selection criteria: (1) identified by the participating patient who consented to approach their caregiver; (2) male or female aged ≥ 18 years who had a personal relationship with and/or provided unpaid support/care for someone diagnosed with *RPGR*-associated XLRP (e.g. spouse, other relative, friend); (3) provided support or care for ≥ 1 h per week (this threshold was suggested by healthcare providers and patients involved in designing the study and was based on pragmatic observation that caregivers with regular contact with the patient could have valuable experience with the patient and their disease); (4) for patients with more than one caregiver, the most impacted/involved caregiver (the main support person) was selected by the patient; (5) able and willing to give informed consent. Each caregiver was interviewed regarding only one patient, even in cases of caring for more. To limit potential bias in results, participants could not enrol as both a patient and a caregiver in the study.

Data were collected from caregivers via cross-sectional surveys managed through remote interviews by qualified personnel at a call centre or at the participating site if local regulations did not allow remote survey interviews via a call centre. Cross-sectional surveys consisted of four caregiver-reported outcome scales: (1) Caregiver Global Impression (CGI) of Patient's Mobility and Daily Activity; (2) European Quality of Life 5-Dimension 5-Level Questionnaire (EQ-5D-5L); (3) Modified Caregiver Well-being Scale–Short Form (CWBS-SF); (4) Hospital Anxiety and Depression Scale (HADS). All instructions (including recall periods) of the four caregiver-reported outcome scales followed the referred publications. A long-term impact caregiver questionnaire (LICQ) was also developed by the sponsor for this study. Caregivers were permitted to decline participation in one or more surveys. User agreements were signed

with all external copyright holders (EQ-5D-5L, HADS, CWBS-SF).

The CGI of the Patient's Mobility and Daily Activity measures impacts of vision problems on the patient's mobility (e.g. walking outside, crossing the street, travelling) and daily activities (e.g. watching television, recognising people, reading), respectively, as assessed by the caregiver. Each measure consists of one item, scored on a 5-point scale ranging from 1 ('not at all') to 5 ('very much'); higher scores indicate greater impact. Recall period was 7 days [21].

The EQ-5D-5L consists of two main parts: the descriptive system and the EQ-VAS (visual analogue scale). The descriptive system comprises five questions measuring health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses to each question are rated on a 5-point scale ranging from 1 (no problem/experience) to 5 (unable/extreme experience) and converted to an index score where 1 is perfect health and < 1 represents less than perfect health. Lower scores indicate a lower health status. The EQ-VAS has a single question for which participants choose a point on the scale from 0 ('the worst health you can imagine') to 100 ('the best health you can imagine'). Higher scores indicate better self-perceived health. Recall period was the day of the survey [22].

The CWBS-SF assesses the extent to which a caregiver's basic human needs (physical, emotional, self-security) are being met and the extent to which a caregiver can satisfactorily meet their predictable activities of daily living (self-care, connections, time for self). The original CWBS-SF was a 16-item scale [23]; however, per the latest version of the CWBS-SF, a modified 14-item scale was used (activities of daily living, 8 items; basic human needs, 6 items), with each item rated on a 5-point scale ranging from 1 ('rarely') to 5 ('usually'). Lower scores indicate lower well-being. Recall period was 3 months [23, 24].

The HADS measures symptoms of anxiety and depression and comprises seven items, each with depression and anxiety subscales. Scoring for each item ranges from 0 to 3, with 3 denoting the highest anxiety or depression level. A total subscale score > 7 points out of a possible 21 denotes considerable symptoms of anxiety or depression. Recall period was 7 days [25, 26].

The LICQ was developed by the sponsor based on inputs from healthcare providers and patients to complement data collected from the caregiver-reported outcome scales in both scope and recall period. It covers four areas of interest: (1) caregiver socio-demographics; (2) caregiver health-status information; (3) financial impact of the disease; (4) additional information on the patient's healthcare-resource utilisation. The 1-year recall period for the LICQ for questions other than the current demographic and employment status questions was defined based on inputs from the healthcare professionals and the patients involved in designing the study, and was based on pragmatic considerations to assess longer-term impact on the disease but also to minimise the potential memory effect bias.

Patients who were supported by caregivers were categorised as 'mild', 'moderate' or 'severe' by their physician, based on visual acuity and visual field diameter measurements in accordance with the 'Visual Standards—Aspects and Ranges of Vision Loss' report from the International Council of Ophthalmology [27]. Caregiver survey results were tested for relationship to patients' stage of XLRP, but only significant correlations are described herein.

Data were summarised using descriptive statistics. Continuous/ordinal variables were summarised using number of caregivers (n), mean, standard deviation (SD), median, minimum, maximum and 95% confidence interval (CI). Categorical variables were summarised with n , percent and 95% CI. No truncation of negative lower CI value to 0 has taken place. Correlations between level of disease stage and level of burden were analysed exploratively using appropriate correlation methods, and all reported p -values were non-adjusted, nominal and exploratory in nature.

For relationship of patients' stage of XLRP with continuous/ordinal variables from caregiver survey results, descriptive statistics are provided for the overall population as well as for each category of stage of XLRP. Correlation between stage of XLRP and continuous/ordinal variable was analysed and Kendall τ_b or τ_c rank correlation coefficient with corresponding p -value were provided, depending on the type of variable.

For relationship of patients' stage of XLRP with nominal variables from caregiver survey

results (e.g. type of employment: full-time paid, part-time paid, etc.), frequency distribution (number and percentage with corresponding 95% CI) was provided for each categorical variable by stage of XLRP. Correlations between stage of XLRP and binomial variables (e.g. yes/no responses, such as 'XLRP had impact on level of education') were analysed and rank-biserial correlation coefficients (a measure of association estimated by Goodman–Kruskal's gamma) with corresponding p -value were provided.

The patient portion of our study used the Modified Per Protocol (mPP) patient analysis set of 169 patients who completed at least one patient-reported outcome, did not discontinue for withdrawal reasons and satisfied all inclusion/exclusion criteria. The caregiver analysis set, Modified Per Protocol Analysis Set for Caregivers (mPP_C), comprised individuals who took care of an mPP participant and satisfied all inclusion/exclusion criteria for caregivers.

RESULTS

Key Caregiver and Patient Characteristics

Of 70 caregivers who were enrolled in this study, one cared for a patient excluded from the mPP and one cared for a patient missing clinical staging data, so a total of 68 were included in the mPP_C (Table 1). Mean (SD) age of caregivers was 49.4 (11.7) years and most were female (87.7%). This is compared with the patients they care for ($N=68$), whose mean (SD) age was 36.5 (20.3) years. The mean (SD) age of patients with mild, moderate and severe disease was 30.0 (17.1), 35.5 (16.4) and 43.2 (24.2), respectively. Caregivers were usually either spouses (50.8%) or parents (41.5%) of the patients. Among them, 53 (77.9%) were caring for adults and 15 (22.1%) for adolescents.

Overall, 65 caregivers provided responses to the CGI of Patient's Mobility and Daily Activities questionnaires (Table 1). Caregivers reported overall 78.5% and 86.2% of patients showing any level of impact on mobility and daily activities, respectively. Caregivers' impressions of impact of patients' vision on

Table 1 Characteristics of caregivers (mPP_C) and patients (as reported by caregivers)

Characteristic	N=65
Caregiver age, years	
Mean (SD)	49.4 (11.7)
95% CI	46.5, 52.3
Kendall's τ_b (95% CI)	0.1732 (0.0091, 0.3282)
<i>p</i> -value	0.0387
Female, <i>n</i> (%)	57 (87.7)
Male, <i>n</i> (%)	8 (12.3)
Relationship to patient, <i>n</i> (%)	
Parent	27 (41.5)
Spouse	33 (50.8)
Child	2 (3.1)
Brother	0
Sister	1 (1.5)
Friend	2 (3.1)
Age group of patients cared for, <i>n</i> (%) ^a	
Adult	53 (77.9)
Adolescent	15 (22.1)
CGI of Patient's Mobility ^b , score	
Mean (SD)	3.1 (1.5)
95% CI	2.8, 3.5
Kendall's τ_c (95% CI)	0.2535 (0.0342, 0.4728)
<i>p</i> -value	0.0235
Caregiver responses, <i>n</i> (%)	
Not at all	14 (21.5)
A little bit	10 (15.4)
Somewhat	11 (16.9)
Quite a bit	16 (24.6)
Very much	14 (21.5)
CGI of Patient's Daily Activities ^b , score	
Mean (SD)	3.2 (1.4)
95% CI	2.9, 3.6

Table 1 continued

Characteristic	N=65
Kendall's τ_c (95% CI)	0.1867 (−0.0254, 0.3989)
<i>p</i> -value	0.0845
Caregiver responses, <i>n</i> (%)	
Not at all	9 (13.8)
A little bit	15 (23.1)
Somewhat	12 (18.5)
Quite a bit	12 (18.5)
Very much	17 (26.2)

N for each parameter reflects non-missing values

CGI Caregiver Global Impression; CI confidence interval, mPP_C Modified Per Protocol Analysis Set for Caregivers; SD standard deviation

^a*N*=68 for age group of patients. ^bFor CGI scores, 1 represents the lowest impact and 5 represents the highest impact

mobility were significantly positively correlated with clinical stage of XLRP, with patients with severe disease tending to be more greatly impacted than patients with mild disease.

Outcomes from Caregiver Self-Reported Surveys

EQ-5D-5L

Average EQ-5D-5L index and EQ-5D-5L visual analogue scale (EQ-VAS) scores are shown in Table 2 for the caregivers who responded. Overall outcomes suggest a health status in the range of the population norms for this scale (see Discussion). Across the five domains of the EQ-5D-5L, only caregivers of patients with moderate or severe XLRP reported severe or extreme problems with usual activities, pain or discomfort, and anxiety or depression (Supplementary Table S1). The 'Pain/Discomfort' and 'Anxiety/Depression' domains showed the greatest impacts, with only 56.3% of all caregivers reporting no pain or discomfort, and

only 54.7% reporting they were not anxious or depressed (Supplementary Table S1).

CWBS-SF

A total of 64 caregivers provided responses to the CWBS-SF questionnaire. CWBS-SF scores for activities of daily living can range from 8 to 40, and the overall mean (SD) score for these caregivers was 29.9 (6.1), indicating that overall activities were being met almost frequently. Similarly, the potential score range for basic human needs is between 6 and 30, and the overall mean (SD) score for this study was 23.9 (4.6), again indicating that these caregivers were meeting their basic human needs almost frequently (Table 3).

HADS

Of the 65 caregivers who responded to the HADS questionnaire, most scored within normal or mild ranges for both depression and anxiety (Table 4). Among caregivers, 23.1% reported any level of depression, with 4.6% and 3.1% reporting scores indicating moderate and severe depression, respectively. Additionally, 46.2% of caregivers reported any level of anxiety, with 18.5% and 4.6% reporting scores indicating moderate and severe anxiety, respectively.

LICQ

A total of 65 caregivers provided responses to the LICQ. Caregivers reported a mean (SD) of 28.7 (34.6) and median of 15.0 h spent per week caring for the patient in the past year, which significantly positively correlated with the clinical stage of the patients' XLRP. Caregivers of patients with severe disease reported spending a mean (SD) of 38.1 (41.2) hours per week caregiving (Table 5). Most caregivers reported no change, or an increase, in caregiving involvement over the last year. Most of the support provided by caregivers over the last year was categorised as emotional (84.1%), travel (79.4%), daily activities (79.4%) and financial (60.3%).

Caregivers were asked to rate on a scale of 1 (negative) to 5 (positive) how being a caregiver impacted their life regarding their health, career, finances, education and emotional state. Overall, a score of 3 (indicating no impact) was given by caregivers for health (54.1%), career (53.3%), finances (50.0%), education (52.5%) and emotional state (36.5%). However, some caregivers reported negative impacts (scores of 1 or 2) in each of these domains: health (26.3%), career (28.3%), finances (27.4%), education (25.4%) and emotional state (33.4%).

Overall, 72.3% of caregivers reported being employed (Table 5). Although there was a trend of fewer caregivers being employed when taking care of patients at more severe disease stages, there was no significant correlation between employment status and clinical stage. Half of employed caregivers worked full time, 34.8% worked part time, and 13.0% were self-employed. Fifteen of the 18 unemployed caregivers responded to the question regarding the reason for their unemployment, with 33.3% reporting their unemployment was due to caregiving responsibilities. Of all participating caregivers, 21.9% reported that caregiving impacted their work or job in the past year. The most frequently reported impacts were reductions in working hours, salary and responsibilities. The days missed from work in the past year due to caring for patients with XLRP remained very low (mean [SD], 2.9 [6.7] days).

Caregivers were asked about the effect of the patient's XLRP on their work productivity and on their ability to do regular daily activities using a 10-point scale (0=no effect, 10=completely prevented from working; Table 5). For work productivity, 44.6% of caregivers reported no impact, with an average (SD) overall score of 1.95 (2.37), reflecting limited impact. For regular daily activities, 29.2% of caregivers reported no impact, with an average (SD) overall score of 2.86 (2.59), again indicating low impact.

Table 2 Caregiver EQ-5D-5L and EQ-VAS outcomes

EQ-5D-5L index score ^a (<i>N</i> = 64)	
Mean (SD)	0.81 (0.20)
95% CI	0.76, 0.86
Kendall's τ_b (95% CI)	−0.00549 (−0.1705, 0.1610)
<i>p</i> -value	0.9543
EQ-VAS score ^b (<i>N</i> = 63)	
Mean (SD)	80.8 (15.6)
95% CI	76.9, 84.7
Kendall's τ_b rank	−0.0282 (−0.1944, 0.1395)
<i>p</i> -value	0.7427

N for each parameter reflects non-missing values
CI confidence interval; *EQ-5D-5L* European Quality of Life 5-Dimension 5-Level Questionnaire; *EQ-VAS*, EQ-5D-5L visual analogue scale; *SD* standard deviation
^aFor the EQ-5D-5L index score, 1 represents perfect health and < 1 represents less than perfect health. ^bFor the EQ-VAS score, 0 represents ‘the worst health you can imagine’ and 100 represents ‘the best health you can imagine’

DISCUSSION

To our knowledge, this is the first real-world study across multiple countries in Europe and Israel to collect data from caregivers about the impact of caring for patients with XLRP caused by the *RPGR* variant. In our study cohort, caregivers reported varied impacts on their lives. The mean (SD) age of caregivers completing the surveys was 49.4 (11.7) years compared with 36.5 (20.3) years for the patients they cared for (*N* = 68). Caregivers were mainly female (87.7%) and the patients they cared for mainly male (91.2%) [20]. We found a significant correlation between clinical stage of patients’ XLRP and time spent providing care. Overall, the mean (SD) time spent providing care was 28.7 (34.5) h per week, which is higher than seen in other reports on time spent providing care for patients with visual impairments: Varadaraj et al. reported an average of 100.3 h per month (approximately 23.4 h per week) caring for elderly patients with self-reported visual impairment [5], and Khan et al. reported an average of

2.2 h per day (approximately 15.4 h per week) caring for patients with visual impairment due to macular degeneration or diabetic retinopathy [4]. In our study, caregivers of patients with severe XLRP were especially burdened, as they spent a mean (SD) 38.1 (41.2) hours per week providing care, which is a time investment comparable to a full-time job. This finding is not surprising, given that patients with more severe disease are likely to need more support for tasks requiring vision, such as travel and healthcare visits. Indeed, the CGI mobility data corroborate this finding, with patients at the severe stage tending to report worse scores than patients with mild disease, according to their caregiver. However, just over a fifth of caregivers reported an impact on their work, and few days of work were missed per year on average, suggesting that time spent caring is coming out of personal time, potentially impacting social and leisure activities, which we would expect to have detrimental impacts on well-being of caregivers in our study [4, 6].

Despite the reported overall hours of caregiving and their increase by disease stage, we found limited impacts on well-being and health according to the CWBS-SF, EQ-5D-5L and EQ-VAS. The average EQ-5D-5L index score of caregivers was slightly worse than population norms reported for Germany, France and Belgium [28–30]. In contrast, the overall average EQ-VAS rating was slightly better than population norms reported for those three countries [28–30]. Of note, only caregivers of patients with moderate or severe XLRP reported severe or extreme problems with usual activities, pain or discomfort, and anxiety or depression. However, the overall percent of ‘no problem’ responses was better in our study for three domains compared with the population norms of France and Belgium, including for pain/discomfort; our percentage of ‘no problem’ responses for usual activities and anxiety/depression was similar to population norms from France but worse than those from Belgium [29, 30]. Given the very limited impacts reported using these tools, it is plausible that they are not appropriate to capture the extent of the burden on caregivers for patients with XLRP. This is, perhaps, not surprising, given that the EQ-5D has been criticised for

Table 3 Caregiver CWBS-SF scores ($N = 64$)

Activities of daily living ^a	
Mean (SD)	29.9 (6.1)
95% CI	28.5, 31.6
Median	29.5
Kendall's τ_b (95% CI)	0.1637 (−0.0021, 0.3207)
p -value	0.0529
Basic human needs ^b	
Mean (SD)	23.9 (4.6)
95% CI	22.8, 25.1
Median	25.0
Kendall's τ_b (95% CI)	0.0437 (−0.1230, 0.2079)
p -value	0.6087
Total score ^c	
Mean (SD)	53.8 (9.7)
95% CI	51.6, 56.4
Median	54.5
Kendall's τ_b (95% CI)	0.1214 (−0.0452, 0.2815)
p -value	0.1528

N for each parameter reflects non-missing values. Responses for CWBS-SF are rated on a 5-point scale ranging from 'rarely' to 'usually', where lower scores indicate lower well-being

CI confidence interval; CWBS-SF Modified Caregiver Well-being Scale–Short Form; SD standard deviation

Possible score range for each measure: ^a8 to 40 for activities of daily living; ^b6 to 30 for basic human needs; ^c14 to 70 for total score

lacking sensitivity to the impairment of people with low vision [31]. If the tool cannot discriminate ability levels among those with low vision, then it may also be of limited use with the caregivers of people with visual impairments. On the other hand, in studies like ours, there might be a selection bias of participants—caregivers who

Table 4 Caregiver HADS scores^a ($N = 65$)

HADS–depression	
Mean (SD)	5.0 (3.8)
95% CI	4.0, 5.9
Kendall's τ_b (95% CI)	0.0006 (−0.1638, 0.1650)
p -value	0.9942
Caregiver responses, n (%)	
Normal (≤ 7)	50 (76.9)
Mild (8–10)	10 (15.4)
Moderate (11–14)	3 (4.6)
Severe (15–21)	2 (3.1)
HADS–anxiety	
Mean (SD)	7.2 (4.1)
95% CI	6.2, 8.2
Kendall's τ_b (95% CI)	−0.1264 (−0.2849, 0.0388)
p -value	0.1332
Caregiver responses, n (%)	
Normal (≤ 7)	35 (53.8)
Mild (8–10)	15 (23.1)
Moderate (11–14)	12 (18.5)
Severe (15–21)	3 (4.6)

N for each parameter reflects non-missing values

CI confidence interval; HADS Hospital Anxiety and Depression Scale; SD standard deviation

^aA total subscale score > 7 points out of a possible 21 denotes considerable symptoms of anxiety or depression

are willing to undergo an additional task in their daily life, such as responding to a scientific survey, might be those who do not feel the highest amount of burden in their lives, while caregivers who are at the limit of their daily life burden may not respond to surveys.

Almost a quarter of caregivers had any level of depression according to the HADS (score ≥ 8), yet overall mean scores did not meet the definition of depression. Notably, the overall mean score was similar to the population norm reported

Table 5 LICQ scores

Average number of hours spent on caregiving per week in the last year ($N = 57$)	
Mean (SD)	28.7 (34.5)
95% CI	19.5, 37.8
Median	15.0
Range	0, 168
Mean (SD) by patients' disease stage	
Mild	22.1 (35.8)
Moderate	22.4 (18.5)
Severe	38.1 (41.2)
Kendall's τ_b (95% CI)	0.2187 (0.0443, 0.3802)
p -value	0.0143
Currently employed (Yes/No) ($N = 65$)	
Yes, n (%)	47 (72.3)
95% CI	59.8, 82.7
No, n (%)	18 (27.7)
95% CI	17.3, 40.2
Correlation with clinical-stage rank-biserial correlation coefficient (95% CI)	− 0.1429 (− 0.5849, 0.2992)
p -value	0.5290
If not employed, is it due to caregiving responsibilities and not COVID (Yes/No)? ($N = 15$)	
Yes, n (%)	5 (33.3)
95% CI	11.8, 61.6
No, n (%)	10 (66.7)
95% CI	38.4, 88.2
Type of employment ($N = 46$)	
Full-time paid, n (%)	23 (50.0)
95% CI	32.7, 67.3
Part-time paid, n (%)	16 (34.8)
95% CI	20.0, 53.2
Self-employed, n (%)	6 (13.0)
95% CI	5.0, 29.9
Other, n (%)	1 (2.2)
95% CI	0.3, 15.5

Table 5 continued

Patient's XLRP impacted caregiver's work/job in any way in the past year ($N = 64$)	
Yes, n (%)	14 (21.9)
95% CI	12.5, 34.0
No, n (%)	50 (78.1)
95% CI	66.0, 87.5
Correlation with clinical-stage rank-biserial correlation coefficient (95% CI)	− 0.0840 (− 0.5232, 0.3552)
p -value	0.7093
If Yes, the way it was impacted ($N = 14$)	
Reduction in work hours, n (%)	10 (71.4)
Up to 30%	8 (80.0)
> 30% and up to 50%	2 (20.0)
Reduction in salary, n (%)	4 (28.6)
Up to 10%	1 (25.0)
> 10% up to 20%	1 (25.0)
> 20%	2 (50.0)
Reduction in responsibilities, n (%)	2 (14.3)
Losing your job, n (%)	1 (7.1)
Other, n (%)	4 (28.6)
Number of days missed from work in the past year because of friend's/relative's XLRP ($n = 60$)	
Mean (SD)	2.9 (6.7)
95% CI	1.2, 4.7
Median	0.0
Range	0, 42
Correlation with clinical-stage Kendall's τ_b rank correlation coefficient (95% CI)	0.0176 (− 0.1543, 0.1884)
p -value	0.8423
Effect of friend's/relative's XLRP on caregiver's productivity while working, in the past year (0 = no effect, 10 = completely prevented from working) ($n = 56$)	
Mean (SD)	2.0 (2.4)
95% CI	1.3, 2.6
Scale responses, n (%)	
0	25 (44.6)
1	6 (10.7)

Table 5 continued

2	3 (5.4)
3	11 (19.6)
4	2 (3.6)
5	4 (7.1)
6	3 (5.4)
7	0
8	1 (1.8)
9	0
10	1 (1.8)
Correlation with clinical-stage Kendall's τ_c rank correlation coefficient (95% CI)	− 0.0172 (− 0.2384, 0.2040)
<i>p</i> -value	0.8787

CI confidence interval; *LICQ* long-term impact caregiver questionnaire; *SD* standard deviation; *XLRP* X-linked retinitis pigmentosa

in Germany, as was the percentage of scores > 8 [32]. The overall mean depression score was higher than population norms reported for the UK, but the percentage of individuals with ‘probable clinical depression’ (score ≥ 11) was higher in the general UK population (11%) than in our study (8%) [33]. Together, these data imply that the caregivers in this study were comparatively normal in terms of depression, as reported with HADS.

Levels of reported anxiety using HADS are typically higher than those of depression, and this was also observed in our study, with 46.2% reporting any level of anxiety (score ≥ 8). The overall mean score was below the scale threshold but was higher than population norms in the UK and Germany [32, 33]. Moreover, the percentage of individuals with ‘probable clinical anxiety’ (score ≥ 11) was higher in our study (23%) than in the general UK population (14%) [33], and the percentage of scores > 8 was higher in our study than in the general German population [32]. Together, these results suggest a degree of impact among the participating caregivers. Loss of leisure time [4, 6] and a lack of emotional support [34] could contribute to higher anxiety relative to population norms for caregivers of patients with XLRP.

One limitation of this study is a lack of a matched cohort to control for effects of age, sex, nation of residence and other factors that might impact reports of well-being. As already mentioned, we cannot ignore the possibility that willing participants for this study may skew towards emotionally stable patient/caregiver dyads who are able to handle the demands of their daily lives. This is compounded by the possibility of a participating patient choosing not to involve their caregiver, further limiting participating caregivers to those with good relationships to the patient. Owing to the low numbers of participating caregivers, both overall and for each of the clinical stages, we were limited in our ability to draw strong conclusions from stage-specific results.

Limitations may also exist in the methods. We acknowledge the scales used have not been validated in this population and have limited and varied recall periods. Although we attempted to overcome the recall period limitation with the LICQ, this questionnaire has not been validated. The interview method may have also introduced bias, as some caregivers may be hesitant to mention how much caregiving responsibilities impacted their health and work, especially if the patient is present during the interview.

CONCLUSION

This study represents the first real-world investigation across multiple European countries and Israel regarding the experiences of caregivers for patients with XLRP due to the *RPGR* variant. The findings reveal that caregivers experience significant variation in the impact of their caregiving and spend a mean of 28.7 h per week on caregiving, particularly pronounced among those caring for patients in more severe stages of the disease. Despite the substantial time commitment, the overall impact on caregivers as measured by the various scales was reported to be relatively limited, suggesting that common assessment tools may not effectively capture the true extent of caregiver burden in this disease. While a significant proportion of caregivers displayed levels of anxiety and a notable fraction reported depression, mean scores remained around the population norms in certain areas. Limitations, including potential selection bias and the absence of a matched cohort, may hinder the generalizability of the results. Future studies should consider refining assessment scales and methods, and exploring the experiences of a broader caregiver population to fully understand the challenges faced by those supporting individuals with XLRP.

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Data Availability. The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Michel Weber, Andrew Lotery, Markus Ritter and Enrique Rodríguez de la Rúa have received consulting fees from Janssen and Novartis. Francesco Parmeggiani has received consulting fees from AbbVie, Bayer, Janssen, Novartis and Roche. Dominique Bremond-Gignac has received consulting fees from Alcon, Janssen, Novartis, Santen and Thea. Avril Daly, Nabin Paudel and Eeva-Marja Sankila have no competing interests. Ygal Rotenstreich has received a consulting fee from Janssen. Katarina Stingl has received consulting fees to the University from Janssen, Novartis, ProQR Therapeutics, Santen, and ViGeneron. Marjolein Lahaye, Jacqueline Van Denderen, Tom Denée, and Katalin Pungor are employees of Johnson and Johnson.

Ethical Approval. The study received local ethical committee approval at each study site (Austria, Ethik Kommission Medizinische Universität Wien: 1088/2022; Belgium, Ethics Committee Research UZ/UK Leuven: B3222022000832; UK, Health Research Authority Integrated Research

Application System: 307690; Finland, HUSin Alueellinen Lääketieteellinen Tutkimuseettinen Toimikunta: 48/2022; France, Comité de Protection des Personnes Nord Ouest IV: 22.02349.000114; Germany, EC Medical Faculty of Eberhard-Karls-University and University Clinic Tübingen: 839/2021BO1, 2022-200343-BO-bet; Israel, EC of the Chaim Cheba Medical Centre: 9186-22-SMC; Israel, EC of the Soroka Medical Center: 0391-21-SOR; Italy, Comitato Ethico di Area Vasta Emilia Centro: 1026/2021/Oss/AOUFe; The Netherlands, Dutch Clinical Research Foundation: 21.177/VS; Spain, Comité de Ética de la Investigación con medicamentos Euskadi: PI2022051) (see Supplementary Table S2 for more details) and adhered to the tenets of the Declaration of Helsinki. All participants gave informed consent.

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