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Systematic Literature Review

Health-Related Quality of Life in Neurological Disorders Most Commonly Associated With Zika-Virus Infection: A Systematic Review

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ABSTRACT

Objectives: In this systematic review, we synthesize the current evidence on health-related quality of life (HRQoL) for the two of the most relevant outcomes of Zika virus infection in humans, microcephaly and Guillain-Barré Syndrome (GBS).

Methods: We searched the following databases: MEDLINE, Embase, CINAHL, LILACS, WHO's ICTRP clinical trials registries database and PROSPERO. Search terms included quality of life, microcephaly, and Guillain-Barré Syndrome. We included primary studies where HRQoL was quantitatively assessed for microcephaly and GBS using validated instruments. We used the Joanna Briggs Institute Critical Appraisal Tools to assess the risk of bias of individual studies.

Results: From a total of 1,657 abstracts screened and 66 full texts reviewed, 21 studies met the eligibility criteria; one study for microcephaly and 20 for GBS. Adjusted disutilities for microcephaly compared to a normative childhood utility ranged from −0.745 to −0.820. For GBS, time traded-off the expected lifetime ranged from 16 days to 3 years. HRQoL follows the clinical course of GBS, with lower scores in the first months, recovery within the first year post onset, and stabilization after one year.

Conclusions: Included studies reported a wide range of HRQoL for GBS, due in part to a high level of heterogeneity in methods, inclusion criteria, follow-up and reporting of results. Opportunities exist for primary studies assessing the longitudinal HRQoL over the entire course of the diseases to inform clinical practice, economic evaluations and health policy.

Keywords: Guillain-Barré syndrome, microcephaly, Zika virus, health-related quality of life, systematic review.

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Introduction

Before the 2015 Zika virus (ZIKV) outbreak in Latin America, little attention had been paid to ZIKV, first discovered in 1947, mainly because of its mild symptoms and short duration, which were similar to other arboviral diseases. Now, however, an association between ZIKV infection and neurologic outcomes such as Guillain-Barré Syndrome (GBS) in infected adults and central nervous system malformation of fetuses in infected pregnant women has been established.[1] A recent systematic review found that microcephaly is the most commonly reported adverse outcome of ZIKV infection, followed by GBS.[2] Estimates of the absolute risk of microcephaly in ZIKV-infected pregnant women vary between 0.95% and 30%,[2] and results from a meta-analysis estimated the risk of GBS in infected adults to be 1.23%.[3]

Microcephaly is characterized by a reduction in the head circumference below 2 standard deviations of the mean for sex, age, and ethnicity[4] and may lead to developmental delays and disabilities, including motor, language, and cognitive development issues.[5]

GBS is an immune-mediated peripheral neuropathy in which cellular and humoral immune responses are triggered by a preceding infection, vaccination, or exposure to toxic substances. Its most common subphenotypes are acute inflammatory demyelinating polyneuropathy (AIDP); acute motor axonal neuropathy (AMAN), which may also be called acute motor and sensory axonal neuropathy (AMSAN) when sensory fibers are affected; and Miller-Fisher's syndrome (MFS).[6] GBS presents clinically as an acute neuropathy characterized by weakness, hyporeflexia, or areflexia, with raised protein concentrations in cerebrospinal fluid and reaching a peak within 4 weeks. Symptoms usually start in the extremities and spread proximally, and approximately 25% of patients require mechanical ventilation because of weakness of the respiratory muscles.[7] Recovery takes weeks to months, residual disability may occur in up to 20% of patients, and fatigue may persist even in patients with good recovery. Mortality ranges from 4% to 15%.[7] Severity of disease and recovery are assessed with the Hughes-disability scale or F-score, a 7-point neurologic assessment scale in which patients are classified as having good recovery (no [F0] or minor [F1] neurologic symptoms and are capable of running),

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moderate recovery (able to walk more than 10 meters without assistance but unable to run [F2]), or severe signs of disease (able to walk 10 meters across an open space with help [F3], bed or chair bound [F4], or mechanical ventilation needed [F5]).[8]

Microcephaly and GBS are expected to have a significant negative impact on patients' health-related quality of life (HRQoL), a concept that reflects individual experiences and perceptions on the physical, psychological, and social domains of health.[9] HRQoL scales have been developed to quantify the burden of illness at the patient and population level. Our study aims to synthesize the evidence on the effects of microcephaly and GBS on HRQoL.

Methods

We conducted this systematic review in accordance with the study protocol registered with the International Prospective Register of Systematic Reviews (CRD42018098882), and we followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[10] An information specialist experienced in systematic reviews designed and conducted the search strategy following the Cochrane systematic review methodology. The initial search was designed in Ovid MEDLINE and subsequently translated into other databases' syntax. It included controlled vocabulary (MeSH) and natural language terms in the following concept areas: quality of life, microcephaly, and Guillain-Barré Syndrome. The full MEDLINE search can be found in Appendix e-1 in Supplemental Materials at https://doi.org/10.1016/j.jval.2020.03.004. We included primary studies (randomized controlled trials, as well as cross-sectional, cohort, and patient preference studies) measuring HRQoL for microcephaly or GBS using validated direct (standard gamble [SG], time trade-off [TTO], and visual analogue scale [VAS]) or indirect (EuroQol-5 dimensions [EQ-5D], Health Utilities Index [HUI], Short Form Health Survey [SF-36], Sickness Impact Profile [SIP], and World Health Organization Quality of Life [WHO-QoL]) instruments. We did not restrict the search in terms of language or publication period, but we excluded editorials, letters, abstracts, and conference proceedings.

We searched the following databases for articles published until July 4, 2019: MEDLINE (Ovid), Embase (Ovid), Cumulative Index of Nursing and Allied Health Literature (CINAHL; part of EBSCO), Latin American and Caribbean Health Sciences Literature (LILACS), and the World Health Organization (WHO)'s International Clinical Trials Registry Platform (ICTRP). We also searched the International Prospective Register of Systematic Reviews (PROSPERO) for all active or completed systematic reviews. Articles included at the full-text screening stage had their references lists checked.

Two reviewers independently screened articles, extracted data, and assessed the quality of the retrieved studies. At the title and abstract screening stage, the reviewers were blinded for the authors' and journal's names. Disagreements were resolved through consensus or by a third reviewer.

We used predesigned, pilot-tested forms for data extraction, including study characteristics (eg, study design, inclusion and exclusion criteria, response rates), patient characteristics (age, sex, stage, and severity of disease), and HRQoL outcomes (utility values and instrument scores). We assessed the quality of the included studies using the Joanna Briggs Institute (JBI) Critical Appraisal tools[11] for overall study design. Additionally, we included questions from a systematic review that summarized specific domains addressing the risk of bias of HRQoL studies[12] because there is currently no quality appraisal tool for HRQoL studies. We did not exclude studies from the final analysis based on study quality.

We planned to conduct a meta-analysis to summarize utility scores for each disorder, but because of the heterogeneity in study designs, valuation methods, patients' characteristics, and stage and severity of disease, performing a meta-analysis was not possible and results are therefore presented and summarized descriptively.

Results

We retrieved a total of 1751 articles from the databases for title and abstract screening; 1657 remained after removing duplicates and 66 articles were included for full-text screening, at which stage 46 studies were excluded (see Appendix e-2 in Supplemental Materials for reasons of exclusions at this stage) and one additional study was identified and included from reviewing references lists (Fig. 1).

We included 21 studies in our review, all published between 1997 and 2016. Of the 21 studies, 1 assessed HRQoL of microcephaly,[13] and the remaining assessed GBS.

The overall quality of the studies was good, with 17 studies (the microcephaly study and 16 of the GBS studies) meeting ≥ 75% of quality appraisal criteria of the JBI tools (Fig. 2; individual results can be found in Appendix e-3 in Supplemental Materials). The main sources of bias identified were small sample sizes, the lack of strategies to address incomplete follow-up in the longitudinal studies, and the absence of a detailed description of the subjects and setting in the cross-sectional studies. None of the preference studies reported on the participation of the patients in previous similar research, which could influence their choices toward specific treatments or health states. Two studies did not perform any pretests for patient's understanding of the instruments used, with the potential of harming the validity of the instruments utilized.

Characteristics of the included studies can be found in Table 1. Table 2 summarizes the findings of the included studies and Table 3 presents the characteristics of the comparator groups in the studies that had one.

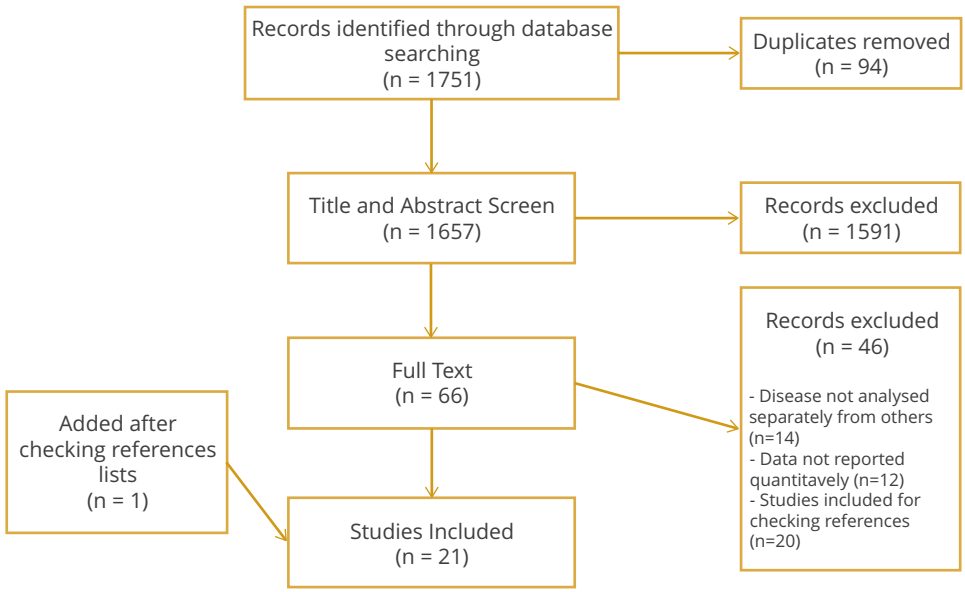
Microcephaly

One study[13] estimated preferences for several diseases in children using the Health Utilities Index 3 (HUI3) with the principal caregivers listed as proxy respondents. The total sample comprised 5600 children, between ages 5 and 16, from a database of more than 200 000 families of children with disability or severe illness in England and Scotland. The sample included 40 children with microcephaly, with a mean age of 11.6 years. Adjusted marginal disutilities for microcephaly ranged from -0.820 (95% confidence interval [CI]: -0.670, -0.970), compared with perfect health, to -0.745 (95% CI: -0.598, -0.899), compared with a normative childhood utility threshold, reflecting the mean HUI3 score of a sample of children of the same age as the study population.

Guillain-Barré Syndrome

Of the 20 studies included for GBS, most are from the United States and the Netherlands with 4 studies each. Three studies from the United States elicited utility values for GBS as a possible adverse effect of influenza vaccination.[14–16] Meanwhile, 2 of the 3 studies from the United Kingdom[17,18] used the same population—a GBS support group. Nevertheless, one study[17] reported on 2 subgroups that had or had not received physiotherapy after hospital discharge, whereas the other one was restricted to participants that reported having a good recovery from the disease (F-scores of 0 or 1 and ability to walk independently without walking aids at the time of the survey). The 2 studies from Sweden used the same group of patients[19,20]; one study followed up patients until 2 years after onset of disease and the other was an update after 10 years of follow-up. Two of the included studies were conducted in Norway,

Figure 1. Flow diagram for study selection.



each in different locations within the country and with different patient groups. The remaining studies were conducted in France, India, Denmark, Australia, Turkey, and Russia.

The most common instrument used in the studies was the SF-36 (n = 8), followed by the SIP (n = 4). The WHO-QoL and the Nottingham Health Profile (NHP) were used in 2 studies, and 1 study each used HUI and SF-12. Four studies used direct methods to estimate utilities, 3 of them used TTO, and 1 used person trade-off (PTO).

Nine of the included studies had no specific inclusion criteria other than the patients being diagnosed with the disease, whereas 5 studies based inclusion criteria on the severity of the disease and 3 studies based inclusion on the condition of the patients after recovery or the acute stage. As for the time of assessment, 6 studies had an assessment point up to 1 year after disease onset, 9 studies at any time between 2 and 9 years, and 4 studies at 10 or more years after onset (Fig. 3). In the longitudinal studies, the time of the follow-up varied between 2 weeks

Figure 2. Risk of bias assessment (percentage of answers to the Joanna Briggs Institute critical appraisal tools).

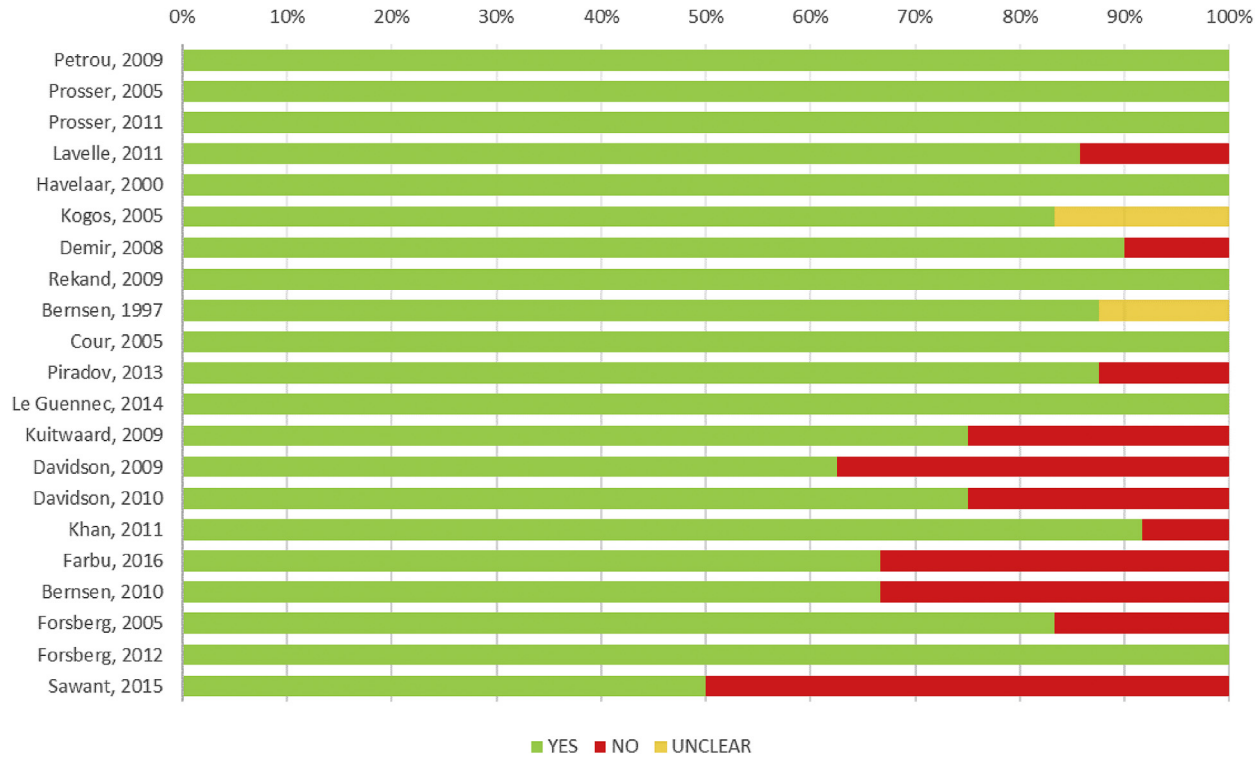


Table 1. Summary of study characteristics.

Author, year (country)	Instruments/ methods	Number of participants	Age/age range (years)	Inclusion criteria	Sample source
Cross-sectional studies					
Petrou, 2009 (UK)[13]	HUI3	40	5-16	Children	Database of 200 000 families of children with disabilities or severe illnesses
Prosser, 2005 (USA)[14]	TTO	112	1*		Adults of a health plan in New England
Prosser, 2011 (USA)[15]	TTO	1012	1, 8, 35, 85*		US adult population
Lavelle, 2011 (USA)[16]	TTO	659	1, 8, 35, 70*		US adult population
Havelaar, 2000 (Netherlands)[34]	PTO	-	-		Panel of medical experts
Kogos, 2005 (USA)[35]	SF-12	18	23-77	Persistent motor deficits at least 1 year after onset of GBS	Patients from 1 medical institution
Demir, 2008 (Turkey)[22]	NHP	31	20-79	F4†	Patients from 1 medical institution
Rekand, 2009 (Norway)[26]	SF-36	50	25-85		Patients from 1 medical institution
Bernsen, 1997 (Netherlands)[25]	SIP	123	NR	≥F4† at baseline	Participants of a multicenter trial
Cour, 2005 (Denmark)[27]	SF-36	40	18-79		Patients in the county of Aarhus
Piradov, 2013 (Russia)[23]	SF-36	75	16-75		Patients from the Moscow region
Le Guennec, 2014 (France)[24]	NHP, SF-36	13	35-78	Patients mechanically ventilated for more than 2 months in the ICU	Patients from 1 medical institution
Kuitwaard, 2009 (Netherlands)[28]	SF-36	245	7-94		Members of a national society of neuromuscular disorders
Davidson, 2009 (UK)[17]	SF-36	742	56-74 (IQR)		Members of a UK GBS support group
Davidson, 2010 (UK)[18]	SF-36	237	49-68 (IQR)	Good recovery from GBS (F0 or F1†)	Members of a UK GBS support group
Longitudinal studies					
Khan, 2011 (Australia)[21]	WHOQoL	69	54.9 (mean)	Long-term symptoms	Patients from 1 medical institution
Farbu, 2016 (Norway)[29]	SF-36	11	34-89		Patients from 1 medical institution
Bernsen, 2010 (Netherlands)[30]	SIP	85	16-88	≥F3†	Participants of a multicenter trial
Forsberg, 2005 (Sweden)[19]	SIP	41	20-80		Patients from 8 medical institutions
Forsberg, 2012 (Sweden)[20]	SIP	29	20-77		Patients from 8 medical institutions
Sawant, 2015 (India)[31]	WHOQoL	23	20-50	F1-F3†	Patients from 1 medical institution

GBS indicates Guillain-Barré syndrome; HUI3, Health Utilities Index 3; ICU, intensive care unit; IQR: interquartile range; NHP, Nottingham Health Profile; NR, not reported; PTO, person trade-off; QoL, quality of life; SD, standard deviation; SF, Short Form Health Survey; SIP, Sickness Impact Profile; TTO, time trade-off; WHOQoL, World Health Organization Quality of Life instrument.
*Hypothetical.
†F-score.

and 10 years from disease onset. Five studies were cohort studies and we only identified one randomized control trial (RCT).[21]

Three studies elicited community values for GBS and presented TTO values from the expected lifetime,[14–16] with a median varying from 60 days to 3 years for a 1 year-old child in undiscounted

Table 2. Summary of findings.

Author, year	Description of results	Findings
Preferences studies		
Petrou, 2009[13]	Adjusted disutilities for microcephaly	−0.82 (from perfect health) −0.745 (from childhood norms)
Prosser, 2005[14]	Median TTO for GBS in a 1-year-old child	3 years (undiscounted analysis) 352 days (discounted analysis)
Prosser, 2011[15]	Median TTO for GBS for individuals of different ages	183 days (1-year-old) 122 days (8-year-old) 16 days (35-year-old) 61 days (85-year-old)
Lavelle, 2011[16]	Median TTO for GBS Median Loss in QALY	30 days (undiscounted analysis) 13.6 days (discounted analysis) 0.0019
Havelaar, 2000[34]	Median severity weights for GBS Mild Severe, < 50 years Severe, ≥ 50 years	1st year of disease / Residual symptoms 0.073/0.019 0.256/0.147 0.335/0.2
HRQoL up to 1 year after GBS onset		
Farbu, 2016[29]	Mean SF-36 scores (patients at onset vs 12 months after)	Physical Component reduction: 65.07% Mental component reduction: 40.2%
Bernsen, 2010[30]	Mean SIP scores (General population vs patients) 3 months after onset 6 months after onset 12 months after onset	Reduction in total scores*: 93.16% 89.87% 87.5%
Forsberg, 2005[19]	Mean SIP scores (vs 2 weeks after onset) 2 months after onset 6 months after onset 1 year after onset	Reduction in total scores*: 43.77% 67.64% 74.8%
Sawant, 2015[31]	Mean WHOQoL-BREF scores (patients at 2 months vs 2 weeks after onset)	Overall reduction in the 4 domains: 37.15%
Demir, 2008[22]	Mean NHP scores (controls vs patients at 12 months after onset)	Overall reduction*: 77.78%
Piradov, 2013[23]	Mean SF scores (patients vs controls) Less than 1 year after onset	Overall reductions: 13.6%
HRQoL 1 to 5 years after GBS onset		
Forsberg, 2005[19]	Mean SIP scores (vs 2 weeks after onset) 2 years after onset	Reduction in total scores*: 77.19%
Bernsen, 1997[25]	Mean SIP scores (controls vs all patients)	Overall reduction*: 87.73%
Piradov, 2013[23]	Mean SF scores (patients vs controls) Between 1 and 5 years after onset Moderate GBS Severe GBS	Overall reductions: 2.86% 11.37% 13.94%
Le Guennec, 2014[24]	Median SF-36 scores	Overall score: 78.37
HRQoL after 5 years of GBS onset		
Khan, 2011[21]	Median WHOQoL-BREF scores (intervention vs control)	Overall reduction in the 4 domains: 7.72% (intention to treat analysis)
Davidson, 2009[17]	Median SF-36 scores (patients who received physiotherapy vs who did not)	Overall reduction: 8.13%
Cour, 2005[27]	Mean SF-36 summary scores (patients vs controls)	Physical Component reduction: 9.22% Mental Component reduction: 6.62%
Davidson, 2010[18]	Median SF-36 scores (patients with minor vs no residual symptoms)	Overall reduction: 13.59%
Forsberg, 2012[20]	Median SIP scores (patients at 10 vs 2 years after onset)	Reduction in total scores*: 14.29%
Kogos, 2005[35]	Mean SF-12 summary scores	Physical: 30.25 Mental: 54.48
Kuitwaard, 2009[28]	Mean SF-36 scores (patients vs general population)	Overall reduction: 10.4%
Piradov, 2013[23]	Mean SF-scores (patients vs controls) More than 5 years after onset	Overall reductions: 21.37%
Rekand, 2009[26]	Mean SF-36 scores (patients at 11 years after onset vs controls)	Overall reduction: 15.78%

GBS indicates Guillain-Barré syndrome; HRQoL, health-related quality of life; NHP, Nottingham Health Profile; QALY, quality-adjusted life-year; QoL, quality of life; SF, Short Form Health Survey; SIP, Sickness Impact Profile; TTO, time trade-off; WHOQol-BREF, World Health Organization Quality of Life instrument.
*Lower scores of the NHP and SIP indicate better HRQoL. In the remaining instruments, lower scores indicate worse HRQoL.

Table 3. Characteristics of comparators.

Author, year	Sample size	Age/age range	Description	Values/scores*
Demir, 2008[22]	31		Healthy subjects with matched age, sex, and education	7.83
Rekand, 2009[26]	81		Similar sex and age healthy subjects	82.21
Bernsen, 1997[25]	239		Sex and age-matched healthy subjects	0.8
Cour, 2005[27]	40		Comparable healthy subjects	PCS: 55.3 MCS: 55.9
Piradov, 2013[23]	40	22 - 70	Healthy subjects	79.04
Le Guennec, 2014[24]			French population	
Kuitwaard, 2009[28]			Dutch population	
Davidson, 2009[17]	155		Patients who did not receive physiotherapy after hospital discharge	64.89
Davidson, 2010[18]	136	49 – 70 (IQR)	Patients with no residual symptoms	87.11
Khan, 2011[21]	34	55.7 (mean)	Patients receiving a low-intensity rehabilitation program	76.5
Farbu, 2016[29]			12 months follow-up	PCS: 69 MCS: 78.6
Bernsen, 2010[30]			Dutch population	0.8
Forsberg, 2005[19]			2 years follow-up Swedish adult population	8.6 NR
Forsberg, 2012[20]			10 years follow-up Swedish adult population	3.6 NR
Sawant, 2015[31]			2 months follow-up	71.04

IQR indicates interquartile range; NR, not reported; SD, standard deviation.
*Please refer to Table 2 for the description of the values.

analysis, and 26.7 to 352 days in discounted analysis. In undiscounted analyses, TTO values for adults varied from 16 to 30.5 days and for seniors from 28 to 61 days.

Cross-Sectional Studies

The cross-sectional studies conducted up to 1 year after onset of disease[22,23] found a difference in at least some domains of the NHP and the SF-36 when compared with healthy subjects. In total, 2 of the 3 studies conducted from 1 to 6 years after disease onset showed no difference in the SF-36 scores between patients and healthy individuals,[23,24] and 1 study found no difference between patients in good physical condition (F0+F1) and healthy subjects but significant differences in some domains for patients with moderate recovery (F2) and in all domains of the SIP for patients with a severe condition (F3+F4).[25] Studies performed 7 or more years after disease onset[23,26–28] found differences in at least some of the domains when compared with healthy subjects, except for one that did not find any significant differences in the SF-36 categories when compared with the general population.[27]

Longitudinal Studies

From the longitudinal studies included, 3 assessed patients during the entire first year of disease and in this period reported an improvement in the overall quality of life (QoL) and physical domains. For the mental/psychosocial summary scores, one study found improvement in the SF-36 during the first year,[29] whereas the other 2 found significant improvements in the SIP scores during the first 6 months only.[19,30] One study had a follow-up time of 8 weeks after admittance of patients to occupational therapy, and results showed significant improvement in all the domains of the WHO-QoL throughout this period.[31] The study that followed up patients 10 years after diagnosis showed no further improvement in the SIP scores after 2 years.[20] The RCT, conducted in patients 6 years after diagnosis assigned to a low- or high-intensity rehabilitation program, showed no difference in the categories of the WHO-QoL between the 2 groups after 12 months of follow-up.[21]

HRQoL in GBS Compared With Healthy Subjects or General Population

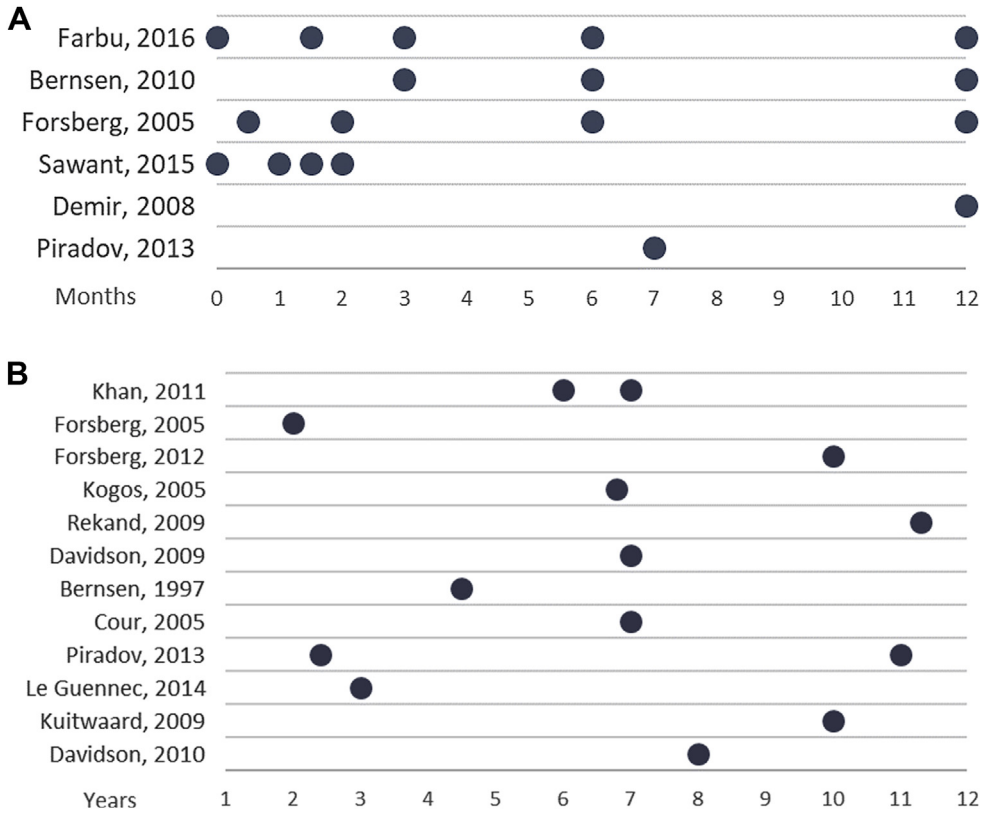
Ten studies reported results with some comparator, either a control group with healthy subjects enrolled in the same study or drawn from population norms. Six of them included patients across the disease spectrum and found a lower quality of life in at least 1 domain of the instruments, even more than 10 years after diagnosis.[19,20,23,26–28] The remaining 4 included only patients with severe disease (F-score ≥F3); 2 of them found differences in all domains of the NHP[22] and the SIP[25]; 1 in the physical, psychosocial, and overall scores of the SIP[30]; and another one did not find any differences in the SF-36 categories compared with the French population.[24] The most commonly affected domains of the SF-36 were "physical function," "role-physical," "general health," and "role-emotional" and for the SIP were "home management," "recreation," "work," and "sleep and rest" categories.

Discussion

This systematic review summarizes studies reporting HRQoL in patients with microcephaly and GBS. We identified only 1 study on microcephaly, a congenital/neonatal disease that leads to mental impairment and developmental issues, with a potentially substantial impact on HRQoL throughout the life span. The lack of HRQoL data for microcephaly is striking. The only study identified in our review included only 40 children with microcephaly, with a mean age of 11 years, from England and Scotland. This paucity of evidence highlights opportunities for longitudinal primary studies to fully assess the impact of microcephaly on HRQoL.

Regarding GBS, our findings show that HRQoL reflects the clinical course of the disease, with a lower HRQoL at the onset of

Figure 3. Time of assessment of the included studies for GBS. (A) Studies with assessment points up to 1 year after disease onset. (B) Studies with assessment points of more than 1 year after disease onset. GBS indicates Guillain-Barré syndrome.



disease followed by improvement during the first year and no changes after. The physical impairment caused by GBS primarily affects the physical and daily activities domains of the HRQoL instruments, and the overall long-term HRQoL in patients can vary substantially depending on their functional status in the postacute phase of the disease.

Although we identified 20 studies for GBS, there is extensive heterogeneity in study designs, methods, instruments, inclusion criteria, comparators, and reporting of results, making it difficult to synthesize the data. We note several knowledge gaps in the literature. Many studies had different primary objectives and assessed HRQoL as secondary outcomes only, which may have had an impact on the resulting HRQoL. Most of the longitudinal studies (4 out of 6) had small sample sizes with less than 50 patients each, which may have harmed the generalizability of their results. Only 3 studies assessed patients during the acute phase of the disease (up to 2 months after onset), limiting our understanding of the impact of GBS on HRQoL during this critical phase. Because of the wide range of clinical presentation across patients, with different severity levels and sequelae in the postacute phase, subgroup analysis in future studies could inform how time and severity of disease can affect HRQoL.

All 3 studies that used direct instruments to elicit preferences for GBS were primarily assessing HRQoL for influenza, with GBS as a vaccine-related adverse event. This, added to the fact that one of them had very discrepant results from the others,[14] demonstrate the need for studies with GBS as their primary focus to refute or corroborate the current findings.

We identified 2 relevant systematic reviews in our searches, 1 of them published in 2010 assessing primarily the effectiveness of multidisciplinary care on adult patients with GBS[32] and the other published in 2014 evaluating the determinants of HRQoL in GBS patients and the domains in which they experience limitations.[33] Our review includes 4 more recent primary studies[23,24,29,31]; 2 of those were longitudinal and followed patients through the first months of the disease, with results reinforcing the previous findings of improvement in HRQoL during this period. Nevertheless, they only assessed HRQoL through the clinical course of the illness and did not have any control group, thus preventing any comparisons between healthy subjects or the general population and showing that important knowledge gaps still remain and should be addressed by future studies.

As a limitation of this review, we cannot exclude the presence of publication bias because we did not search the grey literature for unpublished studies. Nevertheless, we conducted a comprehensive search without any restrictions on language, date, study design and location of the studies. We further followed strict systematic review methods to minimize selection and reporting biases.

Conclusion

This systematic review summarizes HRQoL in patients with the most common neurologic outcomes of the Zika virus infection, and our results can be useful to inform clinical practice, economic evaluations, and policy development regarding any of these illnesses. Our findings demonstrate that the functional and mental impairments in patients with GBS or microcephaly have an impact on their HRQoL. In GBS patients, reported HRQoL tends to reflect the clinical course of the disease with significant improvement

during the first year of disease. Primary studies, however, showed a high level of heterogeneity and we identified critical knowledge gaps in the HRQoL of microcephaly and the long-term HRQoL associated with GBS.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.03.004.

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