Health-Related Quality of Life after Dengue Fever, Morelos, Mexico, 2016–2017

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We adapted the EQ-5D-3L questionnaire and visual analog scale to assess health-related quality of life (HRQOL) and persistent symptoms in 79 patients with laboratory-confirmed dengue in Morelos, Mexico. The lowest HRQOLs were 0.53 and 38.1 (febrile phase). Patients recovered baseline HRQOL in ≈2 months.

Each year, up to 400 million dengue virus (DENV) infections and ≈40,000 deaths occur globally, costing ≈US $9 billion (*1*–*3*). Accurate estimates of disease are needed to track health progress, evaluate prevention and control technologies, and define research priorities (*4*). However, substantial heterogeneity exists in estimates of disease severity and sequelae (*5*). Research suggests dengue symptoms may persist well beyond the acute febrile phase in some patients (*6*–*8*). Little is known about health-related quality of life (HRQOL) for dengue (*7*,*8*). Despite acknowledgement of symptom persistence since 1997 (*9*), most studies focus on the febrile phase, probably substantially underestimating long-term effects of dengue (*2*,*3*,*6*). We investigated HRQOL of dengue patients during their entire laboratory-confirmed dengue episode.

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The Study

All study participants signed informed consent forms. The Ethics Committee of the National Institute of Public Health (project nos. 1223, 1755) approved the study.

We recruited participants with dengue from inpatient and outpatient facilities in Morelos, Mexico, during 2016–2017. Inclusion criteria were age ≥18 years, visit to a healthcare facility 2–6 days after fever onset, laboratory confirmation of DENV infection, permanent residence in Morelos, and a landline telephone. We excluded patients with cognitive impairment, psychiatric diagnoses, specific chronic diseases, and pregnancy. The final sample comprised 79 patients (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/26/4/19-0729-App1.pdf).

Participants underwent a face-to-face questionnaire interview during the febrile phase and were contacted for follow-up regularly for 1 month. After 1 month, participants were contacted until they did not have dengue symptoms or until 6 months after fever onset (Appendix Table 2). Thus, estimates of HRQOL after 1 month constituted only patients with persistent symptoms.

We used an adapted version of a 3-level EQ-5D (EQ-5D-3L) instrument, a standardized method for measuring health status, to measure patients' HRQOL (*10*), including a visual analog scale (EQ-VAS) to estimate self-reported health status. The EQ-5D-3L questionnaire collects information about patient quality of life in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. We also measured quality of life using the EQ-VAS scale (0–100, worst to best health).

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Table 1. Patients with laboratory-confirmed dengue who reported some or extreme problems during the first 30 days after onset of dengue fever symptoms, Morelos, Mexico, 2016–2017*

EQ-5D-3L dimension	No. (%) patients, N = 79			
	Before fever, n = 77	1–6 d, n = 79	7–15 d, n = 71	16–30 d, n = 74
Mobility	1 (1.3)	63 (79.7)	57 (80.3)	59 (79.7)
Self-care	0	43 (54.4)	39 (54.9)	42 (56.8)
Usual activities	2 (2.5)	69 (87.3)	65 (91.5)	65 (87.8)
Pain/discomfort	2 (2.5)	73 (92.4)	66 (93)	63 (85.1)
Anxiety/depression	4 (5.1)	27 (34.2)	28 (39.4)	30 (40.5)

*Patients were >18 years of age. n values indicate number of patients responding to questionnaire during the indicated day range. Health-related quality of life was assessed by an adapted EQ-5D-3L questionnaire (Appendix Table 3, https://wwwnc.cdc.gov/EID/article/26/4/19-0729-App1.pdf) for reporting of problems after 1 month since fever onset (i.e., days 31–60, 61–120, 121–180).

We then created a single EQ-5D-3L index value for the HRQOL (0–1, worst to best health; Appendix Table 4) (*11*). We divided time into day-ranges (0–6, 7–15, 16–30, 31–60, 61–120, and 121–180) because not all participants responded to the questionnaires on the exact same days.

We analyzed changes in HRQOL over time using survival and Cox regression analyses. We defined recovery as baseline HRQOL (before DENV infection) and calculated the time it took each patient to recover. We estimated HRQOL recovery time for subgroups of patients using Kaplan-Meier with log-rank test statistic and identified significant predictors of HRQOL using Cox regression analyses.

The final sample comprised 62% ambulatory and 38% hospitalized patients. Most participants (retrospectively) reported no symptoms before dengue onset. The most affected domains were pain/discomfort, usual activities, and mobility. Almost all participants reported some/extreme problems during the first 6 days (92% pain/discomfort, 87% usual activities, 80% mobility). The proportion of participants reporting problems in any domain increased at 7–15 days after fever onset and remained largely stable until day 30 (Table 1). Among sampled patients, 56% reported dengue-related symptoms ≥30 days; 48%, ≥1 severe symptom; and 73%, ≥1 warning sign. Participants needed an

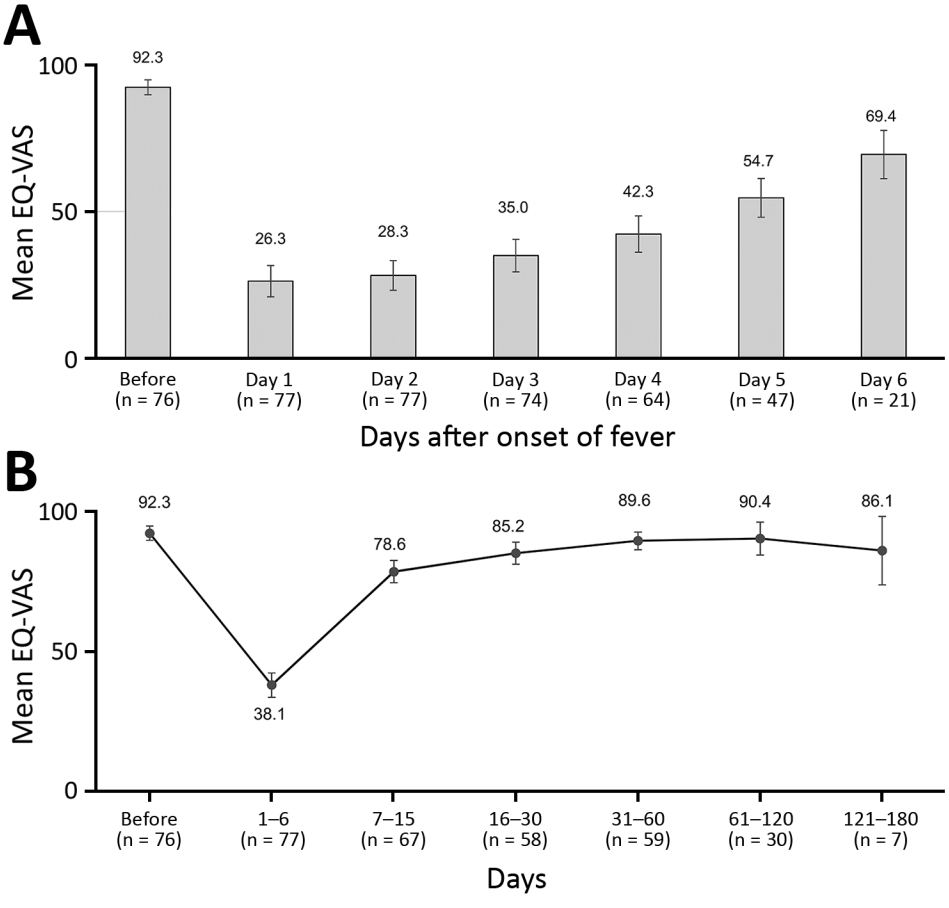

Figure 1. Average self-reported health status, as measured by a 0–100 EQ-VAS, of patients with laboratory-confirmed dengue during the first week after onset of dengue symptoms (A) and from baseline to 121–180 days (B), Morelos, Mexico, 2016–2017. The EQ-VAS scale measures self-reported health, ranging from 0 (worst health status) to 100 (best health status). EQ-VAS is part of the EQ-5D-3L instrument for measuring health-related quality of life. EQ-VAS, visual analog scale. n values indicate number of patients responding to questionnaire during the indicated day range. Error bars indicate 95% CI.

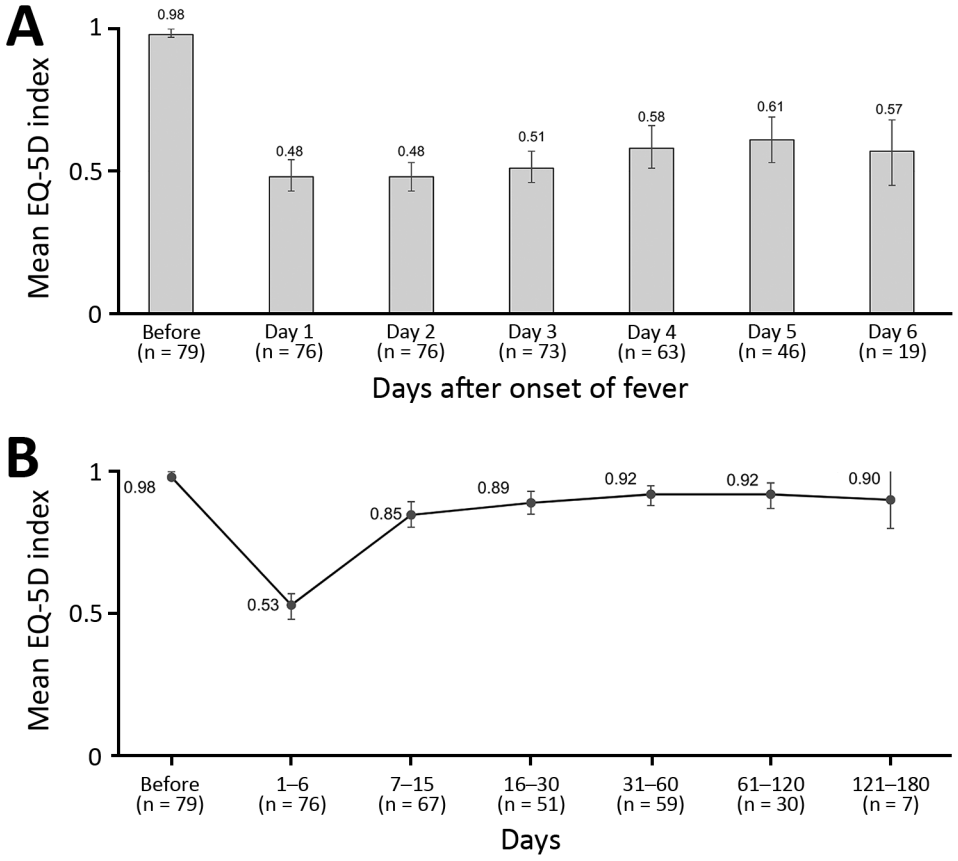

Figure 2. Average health-related quality of life, as measured by the EQ-5D index score, in patients with laboratory-confirmed dengue during days 1–6 of a dengue fever episode (A) and from baseline to 121–180 days (B), Morelos, Mexico, 2016–2017. The EQ-5D scale is a standardized method for measuring health status. n values indicate number of patients responding to questionnaire during the indicated day range. Error bars indicate 95% CI.

average of 46.7 days to completely recover their baseline HRQOL.

We also assessed participants' self-reported health status (EQ-VAS) during the first 6 days (Figure 1, panel A). Participants reported good health at baseline (EQ-VAS 92.3 [95% CI 89.8–94.8]). The worst health was reported during the first day (EQ-VAS 26.3 [95% CI 20.9–31.7]) and second day (EQ-VAS 28.3 [95% CI 23.2–33.3]) and slowly improved until day 6 (EQ-VAS 69.4 [95% CI 61.2–77.7]) but remained well below baseline. When we analyzed the evolution of perceived health until the end of the study (Figure 1, panel B), mean EQ-VAS was 38.1 (95% CI 33.8–42.5) for days 1–6, the lowest observed for any day range. The mean EQ-VAS score then improved until days 61–120 (EQ-VAS 90.4 [95% CI 84.5–96.3]), when it no longer differed significantly from baseline ($\alpha = 0.05$).

We assessed the mean EQ-5D index score before DENV infection (baseline) and during the first 6 days of illness (Figure 2, panel A). Participants showed high baseline scores (EQ-VAS 0.98 [95% CI 0.96–0.99]). The mean EQ-5D index score dropped by >50% to 0.48 (95% CI 0.42–0.49) during the first day and was 0.57 (95% CI 0.46–0.69) on day 6. During the course of the study period, the EQ-VAS was low during the first 6 days (0.53 [95% CI 49–0.58]) and increased to 0.85 (95% CI 0.80–0.89) for days 7–15 (Figure 2, panel B). The index EQ-VAS did not differ significantly from baseline after ≈61 days (0.92 [95% CI 0.88–0.98]).

We tested differences in HRQOL recovery time using Kaplan-Meier curves for individual subgroups (Appendix Figure 1). Survival curves showed slower recovery times for hospitalized participants (≈40% recovered baseline HRQOL) than for ambulatory participants (≈75%) after 30 days ($p = 0.012$). Participants with severe symptoms (≈30%) also showed slower recovery than did participants without severe symptoms (≈75%) after 20 days ($p = 0.001$), as did participants with ≥1 warning signs (≈40%) compared with participants without warning signs (≈85%) after 15 days ($p<0.001$). Participants with higher education had a faster recovery of HRQOL than did participants with less education ($p<0.001$).

We used a Cox regression analysis (Table 2) to identify factors associated with HRQOL recovery (model: proportionality confirmed; mean variance inflation factor = 1.09, all variables variance inflation factor <1.21; final model χ^2 37.8, $p<0.001$; McFadden pseudo-$R^2 = 0.11$). Recovery rates were higher for men than for women (hazard ratio [HR] 1.87; $p = 0.036$),

Table 2. Results of the Cox regression analysis to identify factors associated with recovering baseline health-related quality of life, Morelos, Mexico, 2016–2017

Factor	Hazard ratio (95% CI)	p value
Sex		
F	Referent	
M	1.87 (1.04–3.37)	0.036
Age, y		
≥38	Referent	
18–37	1.74 (0.93–3.23)	0.082
Educational level		
Primary/secondary school	Referent	
High school or higher	2.06 (1.03–4.11)	0.042
Symptoms		
Severe symptoms		
Presence	Referent	
Absence of ≥1	2.82 (1.50–5.33)	0.001
Persistence of symptoms		
No persistence	Referent	
Persistence <30 d	2.28 (1.24–4.19)	0.008
Specific symptoms in the first 15 d		
Presence of specific symptom	Referent	
Absence of skin ache	0.37 (0.19–0.70)	0.002
Absence of scaling skin	0.33 (0.11–0.94)	0.038
Absence of abdominal pain	1.65 (0.79–3.44)	0.182

patients with more education (HR 2.06; p = 0.042), and patients with no severe symptoms (HR 2.82; p = 0.001). In the first 15 days of disease, dengue patients without skin ache had a 63% lower likelihood (HR 0.37; p = 0.002) and patients without scaling had a 67% lower likelihood (HR 0.33, p = 0.038) of recovering to baseline HRQOL.

Conclusions

Dengue significantly reduces HRQOL beyond the febrile phase. Mobility, pain, and usual activities were the most affected domains, consistent with previous studies (*8*,*12*). The proportion of patients reporting problems remained stable among patients with persistent symptoms of dengue. HRQOL decreased abruptly during the febrile phase; most patients then steadily recovered, with some exceptions for those who had not reached baseline HRQOL at 6 months. Other studies have found larger reductions of HRQOL than we found; mean EQ-VAS score was 7 for children 0–14 years of age in Cambodia (*13*) and 10 for hospitalized patients and 20 for ambulatory patients in Brazil (*7*). Our findings were comparable to those of Armien et al. (*14*) in Panama (EQ-VAS 35.2 for children; 31.9 for adults). Female sex was significantly associated with dengue severity in our study, and education (a proxy for socioeconomic status) might be a protective factor. We found skin symptoms to be associated with a faster recovery, possibly because of a lower inflammatory or immune response (*15*).

Our findings are subject to limitations: an adults-only sample; limited socioeconomic characterization of participants; lack of data about previous DENV infections; limitations of the EQ-5D-3L instrument; possible recall bias for baseline HRQOL; response-, recalibration-, and reconceptualization response–shift biases; and a relatively small sample of patients with laboratory-confirmed dengue. Despite these limitations, our findings are relevant for clinical practice and health services research and can help researchers and other stakeholders improve estimates of dengue effects.

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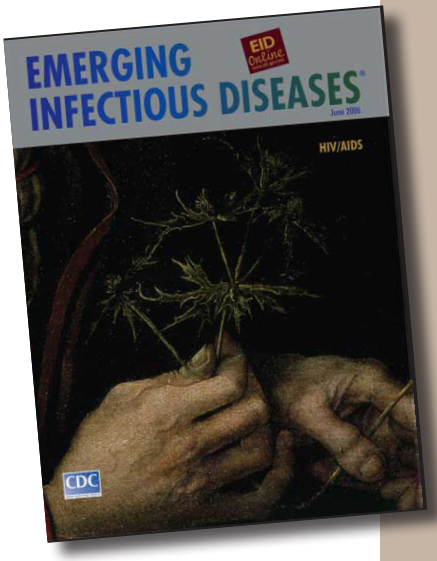

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An acute, self-limited disease characterized by fever, headache, myalgia, and rash caused by any of 4 related but distinct viruses of the genus *Flavivirus* and spread by *Aedes* mosquitoes. Dengue (a Spanish homonym for the Swahili *ki denga pepo*, which describes a sudden, cramplike seizure caused by an evil spirit) is believed to have been first recorded in a Chinese medical encyclopedia from the Chin Dynasty (265–420 AD). The Chinese called dengue "water poison" and knew that it was somehow associated with flying insects.

Sources: Dorland's illustrated medical dictionary. 30th ed. Philadelphia: Saunders; 2003; Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998;11: 480–96; and Halstead SB. Dengue hemorrhagic fever—a public health problem and a field for research. Bull World Health Organ. 1980;58:1–21

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Appendix

Additional Context

Dengue fever has become the most important arbovirus disease worldwide due to a rapid spread in the past 50 years (*1–5*). More than half of the world population is living in high risk areas (*5–8*) and a dengue transmission occurs in at least 140 countries worldwide (*9*). Currently, the World Health Organization (WHO) recognizes dengue as one of the top ten threats of global health in 2019 (*10*). Estimates of the global distribution of dengue incidence are heterogeneous. Combining various data sources, including surveillance records, cohort studies, population, and several covariates in a formal model, researchers estimated »390 million annual dengue virus (DENV) infections (95% CI 284–528). Of these, »96 million infections (95% CI 67–136) showed clinical symptoms (*11*). The majority of these clinical DENV infections go unreported or misdiagnosed (*12–19*). Other studies have estimated 50 to 100 million symptomatic DENV infections annually (*9,20*), with the most recent estimate at 105 million dengue episodes (*21*) and 40,500 deaths (*22*). Despite variation in the specific estimates of symptomatic dengue episodes, there is vast agreement that dengue is a serious threat to public health systems in most tropical and subtropical countries globally (*8,10,23*).

Rigorous, comparable estimates of disease burden are important to track health progress, evaluate prevention and control technologies, and define research priorities (*24,25*). Several researchers have attempted to estimate the disease burden of dengue (*11,15,26–34*). But in addition to differences in how symptomatic cases are estimated, there has been heterogeneity in estimating the severity of the disease and sequelae (*9,34–36*). In addition to the increase in disease burden, recent studies suggest that symptoms in a DENV infection can go beyond the acute self-limiting febrile phase, and present persistent symptoms in some patients, including fatigue, depression, or weight loss (*28,37–45*). Only a few studies investigated the health-related

quality of life (HRQOL) for dengue patients (*37,46,47*). Most studies on the disease burden of dengue, including those that have examined HRQOL in dengue patients, only consider the febrile phase of the illness, despite persistence being acknowledged by WHO since 1997 (*48*), most likely leading to a substantial underestimation of long-term disease burden. To improve current estimations of the disease burden and corresponding economic burden of dengue, studies should take both the febrile and the convalescence phases into consideration (*2,28,49*).

Materials and methods

Sample definition

Participants with dengue were recruited from inpatient and outpatient facilities in 2016–2017 in the state of Morelos, Mexico (*50*). Inclusion criteria were having >18 years of age, the presence of fever between 48 and 144 hours, laboratory-confirmed dengue, a permanent residence, and the availability of a landline telephone. Laboratory confirmation followed the national health secretary's algorithm and guidelines. Patients with cognitive impairment, psychiatric diagnoses, specific chronic diseases (HIV, type 1 diabetes mellitus, multiple sclerosis, lupus and other autoimmune diseases, fibromyalgia, myasthenia, cancers), and pregnancy at recruitment or during the study period were excluded. Of 438 potentially eligible patients, 141 met the inclusion criteria. Of these, 83 had lab-diagnosed dengue. Four patients were excluded during the study because they got pregnant, were unreachable, or voluntarily left the study. The final sample included 79 lab-confirmed dengue patients (Appendix Table 1).

An exhaustive review study by Gómez-Dantés et al. (*29*) on the epidemiology of dengue in Mexico found the incidence of DF and DHF peaked between 10–20, and 15–29 years of age, respectively. However, our sample included only adults ≥18 years of age, for two reasons. First, our study design included follow-up phone calls in which patients had to respond a standardize questionnaire to assess quality of life. While there is a version of EQ-5D for youth (EQ-5D-Y where the lower age limit is 4 years of age), there are no value sets for children and adults (health states are valued differently), and child participants require an adult to respond as a proxy for child's perceived health. This imposes several logistical difficulties for the follow-up. Second, there are several childhood diseases in Mexico that have similar symptoms to dengue, which

would have resulted in a larger number of recruited patients which would have been later confirmed as non-dengue, increasing study costs unnecessarily.

Participants were surveyed at various points in time, from the febrile phase to 1 month after the onset of fever. Follow-up was continued if the patient had persistent symptoms for up to 6 months after the onset of fever (Appendix Table 2). If a participant did not show dengue symptoms during the follow-up interview, she/he was not interviewed in the next round (i.e., the sample size became smaller in time). Estimates of HRQOL thus were limited to patients with persistent symptoms.

Quantifying HRQOL

Patients' HRQOL was measured with an adapted version of the EQ-5D-3L (Spanish version for Mexico) (*51*), including the use of visual analog scale (EQ-VAS) to estimate self-reported health status, which was part of a larger, standardized, structured questionnaire to characterize patients' sociodemographic status and health. The minor adaptation to the EQ-5D-3L consisted in changing two terms of the original questionnaire that are not commonly used in rural Mexico (*lavarme* was changed to *bañarme* and *actividades cotidianas* was changed to *actividades de todos los días*). The EQ-5D-3L questionnaire collects information of the patient's quality of life in five health domains or dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Quality of life was also measured using the EQ-VAS scale, ranging from 0, representing the worse health status, to 100 representing the best health status. Participants used the EQ-VAS scale to represent current health status. We divided time into day ranges, "0 to 6 days," "7 to 15 days," "16 to 30 days," "31 to 60 days," "61 to 120 days," and "121 to 180 days" because not all participants could respond the questionnaires on the exact same days. These day ranges were chosen based on the approximate clinical course of dengue (0–6 and 7–15 are approximately the acute febrile and convalescent phases respectively) and based on previous studies (*37,46*). This choice also guaranteed a sufficient number of participants with completed surveys for each period.

Appendix Table 3 shows the results of health dimensions for the whole study period to complete the already presented data. A large proportion of patients with persistent symptoms (therefore stayed in the study) presented problems mainly in the dimensions pain/discomfort,"

"usual activities," and "mobility in the time ranges 31 to 60 days," "61 to 120 days," and "121 to 180 days" after fever-onset.

To create a single EQ-5D-3L index value for the HRQOL of each patient, the Latin American value set from Zarate et al. (*52*) was used for weighting (Appendix Table 4). To date, there is no specific value set for Mexico available. The value set we used allowed the calculation of 243 different health states, including a social preference weight. The score ranged from 0 to 1 (0 represents the worst and 1 the best health state possible). Participants rated their HRQOL before the onset of dengue during the first interview; this rating was used as a reference value (i.e., baseline) for the description of patient's HRQOL, and we tracked changes in HRQOL over time.

Data Analysis

We analyzed patients' longitudinal data using survival analysis and Cox regressions. For those analyses, the development of a time and status variable is necessary. To create the time variable, we defined recovery as reaching the baseline value of HRQOL and calculated the time of each patient from onset of symptoms to recovery. Within the status variable, censored cases (those who did not reach their baseline value) and non-censored cases were classified. We estimated changes in recovery time of HRQOL for different subgroups using the Kaplan-Meier method with the log-rank test statistic. We tested for proportionality to ensure survival analysis was appropriate. As the survival curves show (Appendix Figure), a slower recovery times is found for hospitalized compared to ambulatory participants after 30 days ($p = 0.012$), for participants with severe symptoms compared to participants without severe symptoms after 20 days ($p = 0.001$), for participants with ≥ 1 warning signs compared to participants without warning signs after 15 days ($p<0.001$) and, last for participants with a higher education had a faster recovery of HRQOL than patients with less education ($p<0.001$).

Finally, we identified significant predictors of HRQOL using Cox regression. We chose relevant variables for the Cox regression based on the scientific literature and the group's clinical expertise in dengue. Based on the size of the study population, a limited number of variables have been added to the model. We checked for multicollinearity using variance inflation factor and the correlation matrix. Significance was defined at $\alpha = 0.05$. We used IBM SPSS Statistics 21 software.

Extended Discussion

The results suggest that dengue fever comes along with a significant reduction of HRQOL beyond the acute febrile phase of disease, consistent with previous research of persistent symptoms. Particularly the dimensions of mobility, pain, and usual activities were the most affected in the first 30 days of the dengue fever episode. These results seem plausible considering the symptoms of the disease. For example, a recent study by Tran et al. (*53*) about dengue patients in Hanoi also suggested that the most affected dimensions of HRQOL were mobility (62.3% of participants), usual activities (64.4% of participants) and self-care (71.8% of participants). The proportion of patients with pain was much lower in the Hanoi study than in our study (32.2% of participants). Tran et al. (*53*) measured quality of life at a single point in time; in contrast we took several measurements during the febrile phase of the disease and after. Another study by Lum et al. (*46*) described the HRQOL in dengue patients in Malaysia in the first 20 days of disease. They found the most affected dimensions were usual activities, pain, cognition, and interpersonal activities. For example, 94% of the study population reported problems in the dimension of pain, consistent with our study, although we used a different instrument to assess HRQOL.

Anxiety and depression have been previously described as symptoms among dengue patients during the febrile phase (*54*). Our study showed that almost 34% of dengue patients had problems with anxiety or depression in the first 6 days of the disease. The frequency of anxiety or depression increased in the following periods up to 40.5%. Other studies have shown even higher rates of anxiety or depression in dengue patients (*54*). One explanation recording to Tran et al. might be the association with increasing media attention on this topic. If increased media attention is a factor for Mexico, it is not clear at this point.

The results of the descriptive health profile showed the percentage of patients that report problems in any of the five dimensions considered by EQ-5D-3L remain stable in patients with persistent symptoms. Our results clearly demonstrated a reduction in HRQOL in the first days of illness. HRQOL increased steadily following the febrile phase, although for some patients, HRQOL had not yet reached baseline value after 6 months. It is relevant to note that because the follow-up was continued only if the patient had persistent symptoms for up to 6 months post

fever-onset, the sample size decreased in time, so direct comparisons of health status may be problematic.

Different results of those measurements of HRQOL of dengue patients exist in the literature. Suaya et al. (*55*) investigated the HRQOL of children with dengue in Cambodia and show a stronger reduction of HRQOL compared to our findings (average EQ-VAS of seven). This may be partially explained because Suaya et al.'s study population were children aged 0 to 14 years old. With a median EQ-VAS of 10 for inpatients and 20 for outpatients, Martelli et al. (*37*) observed a lower HRQOL of dengue patients (adults) in Brazil. Our findings are supported by the results from Armien et al. (*56*). In their study, the median of EQ-VAS was 35.2 for children and 31.9 for adults. All these studies used the EQ-VAS to describe the HRQOL of dengue patients. By using EQ-VAS plus the index score more information was generated. The same pattern emerged from both parts of the EQ-5D-3L and were used to support the results. Just one study identified used the index score in dengue patients. This study among dengue patients (adults) in Hanoi showed a higher index (0.66) compared to our findings (*53*).

Consistent with previous studies (*41,44,57*), we found female gender was associated with persistence of symptoms. There have been heterogenous findings about differences in HRQOL of hospitalized and ambulatory dengue patients. While Martelli et al. (*37*) found evidence for significant differences in those two groups, Tran et al. (*53*) did not. Both studies were cross-sectional (i.e., had only one measurement). We found differences, which seem plausible considering that patients with severe dengue symptoms are commonly hospitalized. These findings are relevant for clinical practice, as they could imply recurrent care for some patients. For patients with persistent symptoms, with at least one severe symptom or warning sign, abdominal pain, persistent vomiting, clinical accumulation of fluids, bleeding in mucosae, lethargy or restlessness, and liver enlargement (*1*), should receive special attention in clinic because of their increased risk of long-term reduction of their HRQOL.

By using a Cox regression we identified several factors that were associated with recovery of HRQOL. Previous research has shown that female gender and older age are significantly associated with severity of dengue episodes (*41,44,57*) and that a higher educational level of dengue patients can be identified as a protective factor (*53,58*). Our findings agree with previous research, but we failed to find a statistically significant correlation between age of the

participant and persistence of symptoms, perhaps due to the relatively small sample size in our study. Discussions about plausible mechanisms to explain those findings are related to the health status and income of patients. Regarding our results, it should be noted that despite the significant p-value, the range of the confidence interval showed a lot of variation in the relative risk of recovering from dengue. Due to that, the effect of gender and educational level on the recovery of HRQOL might be very small.

Our study indicates specific skin symptoms as factors positively affecting the increase in HRQOL over time. This might be explained by the fact that skin symptoms, such as a painful and itchy rash, are linked to the interaction of the virus with the host cells that release various chemical mediators and initiate an immune response (*59*). It is thus assumed that the rash in dengue fever may not be released by the virus, but due to proteins of an intact immune system. Patients with a skin rash do not show more complications or a poorer state of health during the illness than patients without skin rash (*60*). This indicates that a better understanding of skin symptoms in dengue fever is needed to improve diagnosis and treatment (*61*).

The present study has some limitations. The study population includes only adults. Research findings demonstrate differences between adults and children regarding the pattern of complications (*62*,*63*). Because of that, the investigation of the HRQOL in children with dengue fever would be important for both clinical practice, as well as for economic impact. Our findings cannot generalize to the whole Mexican population of dengue patients. Due to our study's restriction to adult patients, our results cannot be directly compared to those other studies with participants in wider age ranges. Further, some variables that may have a significant role in determining HRQOL, such as socio-economic factors, were not included in the questionnaires and could therefore not be investigated. Furthermore, the altitude, for example could not be examined because the study population was homogenous on this characteristic; also, no data were available on prior dengue infections. Although the EQ-5D-3L is a validated instrument, limitations such as ceiling- and floor effects, especially in the descriptive part of the EQ-5D, are possible. Another limitation is a possible recall bias when assessing the baseline value of HRQOL after the onset of the disease. Other potential sources of bias include response-shift, recalibration-response-shift, and reconceptualization-response-shift biases (*64*).

The use of value sets is an important factor in analyzing data of HRQOL. Because there is no Mexican value set available, we used a set based on Latin-Americans living in the U.S. This population may not be representative of the Mexican population. Last, our study population is relatively small and might not be representative of all adult dengue fever patients in Mexico.

This study highlights the relevance of public health research on dengue fever, especially in terms of patient's HRQOL and the persistent symptoms of the disease. The findings of this study are relevant for clinical practice and also for health services research. To accurately estimate the disease and economic burden of dengue, it is important to understand how HRQOL varies in time, beyond the febrile phase of the illness. Such a comprehensive understanding of burden of disease should inform assessments of the disease burden and strategies to control and prevent the disease.

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Appendix Table 1. Descriptive statistics for final sample of lab-confirmed dengue patients in Morelos, Mexico 2016–2017

Characteristic	Hospitalized, no. (%)	Ambulatory, no. (%)
Age, y, n = 79		
18–29	10 (32.3)	21 (67.7)
30–49	13 (35.1)	24 (64.9)
≥50	7 (63.6)	4 (36.4)
Gender, n = 79		
F	14 (31.1)	31 (68.9)
M	16 (47.1)	18 (52.9)
Education, n = 73		
Primary/secondary	20 (37.0)	34 (63.0)
High-school or higher	6 (31.6)	13 (68.4)
Occupation, n = 78		
Student	0	5 (100.0)
In employment/with income	16 (41.0)	23 (59.0)
Not in employment/no income	15 (41.2)	20 (58.8)
Persistence of symptoms, n = 79		
Symptoms ≤30 d	9 (25.7)	26 (74.3)
Symptoms >30 d	21 (47.7)	23 (52.3)
Severity of symptoms, n = 78		
No severe symptoms	9 (22.5)	31 (77.5)
Severe symptoms, at least 1	20 (52.6)	18 (47.4)
Warning signs, n = 79		
Without warning sings	0	21 (100.0)
With warning signs	30 (51.7)	28 (48.3)

Appendix Table 2. Sampling points of the data collection

Month*	Month (1)																												
Week†	Week (1)							Week (2)							Week (3)							Week (4)							
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Activity‡	Visit (1)							Call (1)				Call (2)					Call (3)							Call (4)					
Month*	Month (2)							Month (3)							Month (4)						Month (5)							Month (6)	
Week†	5			6		7		8		9		10		11		12		13		14		15		16		17		18	
Activity‡	Visit (2)			Call (5)				Call (6)				Visit (3)§				Call (7)				Call (8)				Call (9)				Call (10)	

*Month number (1) when subject was recruited.
†Week number.
‡Activity number. Subject's home visit (visit) or subjects contacted by telephone call (call).
§In case of fever persistence.

Appendix Table 3. Share of 79 lab-confirmed dengue patients (>18 y of age) reporting some or extreme problems with health-related quality of life dimensions (adapted EQ-5D-3L) of the whole study period

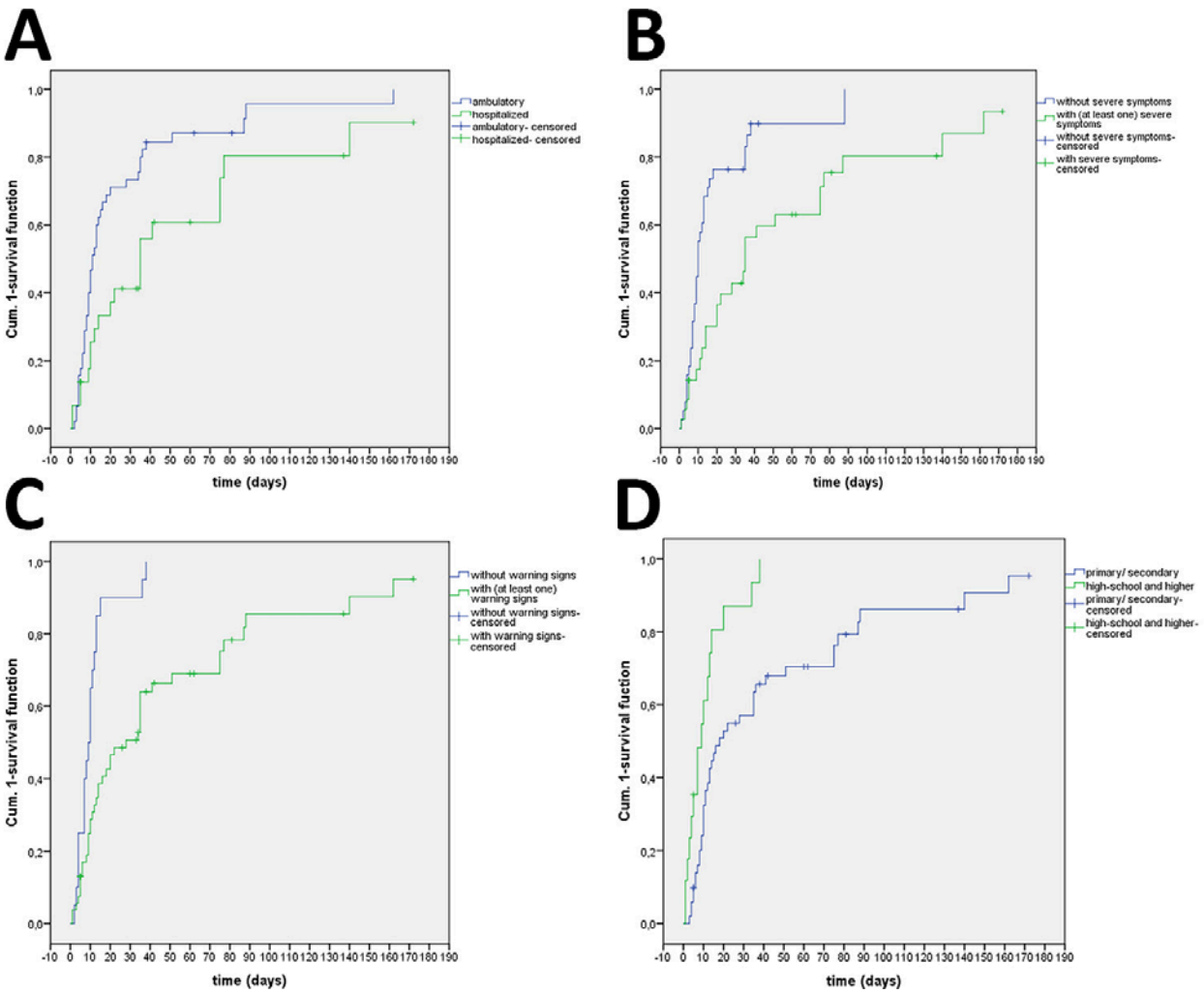
	Days						
Dimensions EQ-5D-3L	Baseline, no. (%)	1–6, no. (%)	7–15, no. (%)	16 –30, no. (%)	31–60, no. (%)	61–120, no. (%)*	121–180, no. (%)*
Mobility	1 (1.3)	63 (79.7)	57 (80.3)	59 (79.7)	53 (85.5)	28 (84.8)	6 (85.7)
Self-care	0	43 (54.4)	39 (54.9)	42 (56.8)	40 (64.5)	22 (66.7)	5 (71.4)
Usual activities	2 (2.5)	69 (87.3)	65 (91.5)	65 (87.8)	57 (91.9)	32 (97)	7 (100)
Pain / discomfort	2 (2.5)	73 (92.4)	66 (93)	63 (85.1)	59 (95.2)	30 (90.9)	7 (100)
Anxiety/depression	4 (5.1)	27 (34.2)	28 (39.4)	30 (40.5)	25 (40.3)	16 (48.5)	4 (57.1)
Total (n)	77	79	71	74	62	33	7

*The proportion of patients presenting some or extreme problems with health-related quality of life dimensions 1 month after the onset of fever or after 1 month, only includes patients who reported symptoms. Patients who reported no symptoms were no longer contacted after the first month and thus did not respond the questionnaire.

Appendix Table 4. N3+X4 model used for calculating the EQ-5D index for each patient with preference weighting*

Parameter	Coefficient	SD	p value
Constant	0.125	0.015	<0.001
M2	0.047	0.012	<0.002
M3	0.290	0.015	<0.003
SC2	0.054	0.012	<0.004
SC3	0.176	0.015	<0.005
Ua2	0.801	0.016	<0.006
Ua3	0.181	0.019	<0.007
Pd2	0.103	0.014	<0.008
Pd3	0.202	0.015	<0.009
Ad2	0.060	0.012	<0.010
Ad3	0.122	0.013	<0.011
N3	0.079	0.018	<0.012
X4	0.074	0.020	<0.013
R^2	0.332		
MAE	0.031		
No (out of 42) >0.05	8		
No (out of 42) >0.10	0		

*Calculations based on Zarate et al. (*52*)



Appendix Figure. Survival curve of lab-confirmed dengue patients in Morelos, Mexico, 2016–2017 comparing (A) ambulatory and hospitalized, (B) with and without severe symptoms, (C) with and without warning signs, and (D) by level of formal education.