Quality of Life of Dengue Patients

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Abstract. Although the disease burden of dengue is increasing, the impact on the quality of life (QoL) has not been investigated. A study to determine the QoL of confirmed dengue patients using the EuroQol visual thermometer scale was carried out at the University Malaya Medical Center. Of the 207 participants, 40% were ambulatory and 60% were hospitalized. Of eight health domains, 6.2 and 5.0 domains were affected in the hospitalized and ambulatory cohorts, respectively (P < 0.001), with cognition and interpersonal activities affected most. All patients experienced a drastic decrease in their QoL from the onset of symptoms. The QoL deteriorated to the lowest point (40% of healthy status) between the third and seventh days of illness. The duration of impaired QoL (9 days for ambulatory or 13 days for hospitalized patients) was longer than the duration of fever (5 and 7 days, respectively). Symptomatic dengue has major effects on patients’ health.

INTRODUCTION

With mosquito vectors and dengue viruses expanding to previously unaffected areas, dengue is becoming the world’s most important arthropod-borne viral infection. A disease of major public health concern, with a global annual average of 829,000 cases and 1,600 deaths officially reported to the World Health Organization (WHO) during the period 2000–2004. However, because dengue is underreported in many countries, researchers have speculated that dengue may cause between 50 and 100 million cases annually, thousands of hospitalizations, and about 20,000 deaths each year.

In Malaysia, dengue was first documented in 1902 and made reportable in 1971. After the first outbreak of dengue hemorrhagic fever (DHF) in 1962, major dengue outbreaks occurred every four years until 1992; since then the disease became endemic with yearly and frequent outbreaks. This situation reflected a phenomenon throughout Southeast Asian cities in which environmental disruption and demographic changes favored proliferation of the mosquito vectors and intense viral transmission, leading to hyperendemicity of dengue and increased incidence of the more severe form (DHF). Malaysia’s reported incidence of dengue has remained high, with an average of 125 to 150 per 100,000 people annually from 2002 to 2006, and the total number of reported cases increasing from approximately 27,000 in 1998 to almost 40,000 in 2005. Most cases were from urban areas.

After several decades of dengue in the urban areas of Malaysia, an epidemiologic shift in peak age incidence of dengue progressed from primarily pediatric ages to predominantly young adults in the 1980s. The proportion of cases ≥ 15 years of age in Malaysia increased from 35% in 1975 to 57% in 1982 and to 78% in 2005. The proportion of dengue-related deaths in persons ≥ 15 years of age in Malaysia similarly increased from 59% in 1996 to 77% in 2005. The phenomenon of predominantly adult dengue population has also been observed in Singapore and Taiwan. Other countries that have reported increased dengue infection in adults include Thailand, Nicaragua, and Sri Lanka but not to the same level as that in Malaysia, Singapore, and Taiwan.

Age-related differences in dengue severity and the characteristics of dengue in the adult population were addressed in reports of cases in Thailand and Nicaragua. The increasing incidence of dengue in older children and adults in Malaysia presents an important opportunity to increase the understanding of the illness from the patient’s perspective and the impact on his or her physical and mental health. Most studies assessing quality of life (QoL) focus on chronic illnesses. The acute illness experienced by dengue patients, although of short duration and not always life-threatening, could have an important impact on the patients’ daily activities, social function, and emotional well-being. Although some dengue studies have examined overall QoL, to our knowledge, this is the first study to examine daily QoL in dengue patients during the entire illness episode.

The data for this study came from a prospective study of the overall effect of dengue illness in the Klang Valley, the region of Malaysia from which most dengue cases are reported. The study included both children and adults treated in either ambulatory or hospitalized settings in a major teaching hospital of Malaysia.

METHODS

Study population. Of Malaysia’s 2005 population of 25.4 million persons, approximately 5.6 million live in Klang Valley where this study was conducted. The study was organized to enroll up to six patients per week recruited from the outpatient or inpatient care at the University Malaya Medical Center. The recruitment period was from December 2004 through December 2005. Selected patients or legal surrogates (when a patient was a child) were invited to participate in this study and a signed informed consent was obtained.

Research instruments. A standardized structured patient survey was developed, piloted, and translated into Malay. It included questions about demographic characteristics of the patient and other household members, as well as relevant clinical characteristics of the illness episode and its effects on health status. The QoL assessment was made using the visual thermometer-like scale (visual analog scale) with 0 representing the worst imaginable health state and 100 denoting best health state from EuroQol, a standardized instrument for valuing health-related QoL. The interviewer showed the thermometer-like scale on the day of enrollment and asked to indicate their level of health by drawing a
line from a box to the point on the scale corresponding to their health state. The participant was then asked to recall how he or she felt and to rate his or her own QoL along the scale on each successive day in the recall period.

Furthermore, a medical record abstraction form was designed to gather clinical and laboratory information needed to classify patients according to the WHO dengue case definition and to confirm the length of patient stay in the hospital. Medical record extraction was used only for hospitalized patients because written records for ambulatory patients were generally very brief or not available.

Data collection, cleaning, and imputations. Patients received two core in-person interviews (initial and follow-up) from one of two trained health interviewers who administered the standardized survey instrument (one interviewer serving ambulatory patients and the other serving hospitalized patients). Each core interview lasted approximately one hour. The initial interview was conducted when the patient first sought care at the ambulatory facility or was admitted in the hospital. The follow-up interview was conducted approximately two weeks later during the last follow-up visit. In addition, to measure QoL, interviewers attempted to conduct daily in-person interviews with all hospitalized patients while hospitalized, and at every follow-up visit. Similarly, they attempted to interview all ambulatory patients at every follow-up visit. Both groups were also reached by phone if more than three days had passed since the last interview. Values for missing days were estimated from linear interpolation.

Analytical framework. The unit of analysis was a confirmed dengue episode, defined by a documented acute febrile illness episode with clinical suspicion of dengue and subsequent laboratory confirmation. Variables of interest included patient’s demographics (age and sex), duration of fever and of the illness episode, symptoms and signs of disease, days of illness by self-reported severity, and self-perceived quality of life, care-seeking behavior, and knowledge of someone else with a concomitant dengue-like illness. The study also calculated each participant’s equivalent number of healthy days lost (HDL) during his or her dengue episode as the sum of his or her reported percentage daily QoL lost by day during the illness episode divided by 100.

Study participants were divided into children (0–12 years of age) and adults (≥13 years of age) according to the standards of medical management at the study facility. The study also classified patients according to the WHO classification into dengue fever (DF) and DHF, including dengue shock syndrome. Because there were a large number of patients with evidence of plasma leakage that failed to be classified as DHF, we classified them as patients with DF and plasma leakage. Analyses were performed in SPSS version 14 (25) and included unweighted means and standard deviations for continuous variables, and frequencies for categorical variables. For analysis of QoL on days without an interview before the last interview, the value was interpolated linearly from adjacent values. If the patient’s last interview occurred earlier than 20 days from the beginning of symptoms, the last QoL measurement was extrapolated through the 20th day.

Ethical considerations. The study protocol was reviewed and approved by the Institutional Review Boards of University Malaya Medical Center, Brandeis University, and the International Vaccine Institute.

RESULTS

The study recruited 235 patients with clinical suspicion of dengue. Of them, 88% (n = 207) had laboratory confirmation for dengue and were included in this analysis. The entire study cohort consisted of 83 participants (40% of enrollees) who received only outpatient care (ambulatory cohort) and 124 participants (60% of enrollees) who also received inpatient care (hospitalized cohort). Females represented 40% of the entire cohort. No deaths were reported among study participants. Patients <1–9 years of age represented 6% and 24% of the ambulatory and hospitalized cohorts, respectively (Table 1). Mean ages were 25 and 21 years among ambulatory and hospitalized patients, respectively.

The study facility considered patients 0–12 years of age as children. Children represented 10% (n = 8) and 38% (n = 47) of the ambulatory and hospitalized cohorts, respectively. Table 2 summarizes the frequency of symptoms and signs by age group and dengue cohort. Gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea were commonly reported in all subgroups of patients but with higher frequencies among the hospitalized patients (all significant at P < 0.001). Low platelet count (< 100 × 10^9/L) (98%), low leukocyte count (< 4 × 10^9/L) (82%), bleeding (64%), and plasma leakage (75%) were common among the hospitalized cohort. Plasma leakage was more common among hospitalized children than adults (94% versus 64%; P < 0.001). However, only 53% and 40% of hospitalized children and adults, respectively, fulfilled the WHO criteria for DHF. The main reason for failing to be labeled as DHF was the lack of bleeding documentation in the medical records.

All patients reported good or very good health status based on a five-point scale before the illness episode. Usual activities had been moderately to extremely affected during the illness episode in most of the patients. All health domains, except vision, were adversely affected, with the hospitalized cohort more often affected. The health domains most affected across all subgroups (range = 85–99%) were cognition and interpersonal activities. Among ambulatory patients mobility and self-care posed the least problems, while these were major issues in hospitalized patients (difference significant at P < 0.001). Adults in the ambulatory cohort were more likely to have pain, discomfort, sleep disorders, and affect symptoms than their pediatric counterparts (Table 3).

In the hospitalized cohort, affect symptoms such as depression were much more common in adults than in children (P < 0.001). For example, 78% of the hospitalized adult patients experienced depression compared with 11% of the hospitalized children. Of eight health domains, 6.2 and 5.0 domains

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of dengue study cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td>Ambulatory (n = 83)</td>
</tr>
<tr>
<td>Female sex</td>
<td>43</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>6</td>
</tr>
<tr>
<td>10–19</td>
<td>25</td>
</tr>
<tr>
<td>20–29</td>
<td>47</td>
</tr>
<tr>
<td>30–39</td>
<td>10</td>
</tr>
<tr>
<td>40–49</td>
<td>8</td>
</tr>
<tr>
<td>≥50</td>
<td>4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25 (11)</td>
</tr>
</tbody>
</table>

* Values are percentages, except for mean (SD).
were affected, on average, in the hospitalized and ambulatory cohort respectively (difference significant at $P < 0.001$).

The QoL during the illness episode was seriously affected in all the subgroups of patients, and its reduction lasted more than 13 days (Figure 1). The overall pattern of the QoL over time was similar across subgroups. All patients had a drastic fall in their QoL coinciding with the onset of symptoms. The QoL deteriorated further over time reaching the lowest point between the third and seventh day of illness. The lowest QoL was close to or below 40% of that associated with a perfect healthy status. Patients then recovered progressively from the lowest reported QoL over the rest of the illness episode. Normal levels of QoL varied by subgroups but were overall achieved after 13 days of illness.

Children in the ambulatory cohort and those hospitalized but without signs of plasma leakage had similar loss of QoL, between the third and seventh day of illness. The lowest QoL was close to or below 40% of that associated with a perfect healthy status. Patients then recovered progressively from the lowest reported QoL over the rest of the illness episode. Normal levels of QoL varied by subgroups but were overall achieved after 13 days of illness.

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and were overall better off than hospitalized children with plasma leakage, in whom a right shift in the trend reflected a worse QoL and a longer time to full recovery (Figure 1A). Hospitalized adult patients without plasma leakage were equally hampered by their disabilities as those who had plasma leakage. The QoL in ambulatory adult patients decreased less each day from onset of illness and recovered sooner than in the hospitalized counterparts (Figure 1B).

Hospitalized patients had, on average, more days of fever (7.1 versus 5.4 days), more days feeling bad or very bad (6.5 versus 3.0 days) and longer duration of illness (12.6 versus 8.6 days) than ambulatory patients (all significant at $P < 0.001$) (Table 4). Interestingly, a larger proportion of hospitalized patients, both children and adults, sought medical care within 24 hours of onset of symptoms than did ambulatory patients (56% versus 39%; $P < 0.005$) (not shown).

Among ambulatory patients, the number of days of fever was similar between children and adults. However, adults had a longer duration of illness and larger number of days feeling bad or very bad than children. Among hospitalized patients, children and adults did not differ in any of these parameters. Children, however, were hospitalized longer than adults ($P = 0.003$). The average number of HDL was similar between children and adults in the ambulatory cohort (4.1 days versus 4.4 days; $P = 0.326$, respectively). In the hospitalized cohort, the HDL was half a day greater in adults than in children (6.2 versus 5.7 days; $P = 0.042$). Overall, the effect of hospitalized cases measured as HDL was approximately 36% greater than that of ambulatory cases (6.0 versus 4.4 days; $P < 0.001$) (Table 4).

**DISCUSSION**

Dengue increasingly affects adults in Malaysia and other countries in the region. The study population was well suited to study this trend, consisting of both children and adults, who received care either outpatient or inpatient care in a major university hospital in the Klang Valley in Malaysia. The age distribution of study participants resembled those of the 2002 dengue cohort, which included all children and adults in both ambulatory and hospitalized settings in the same health facility.23 The age distribution also resembled that of the national dengue data-base in Malaysia, where adults are more commonly affected than children.9 For example, patients ≥10 years of age represented 83% of the study cohort and 89% of the officially reported cases nationally in 2005 and 2006. Children with dengue were more likely to be hospitalized (approximately 80%) than adults (50%). These findings suggest the complex patterns that will evolve as dengue increasingly becomes an adult disease. The predominance of dengue among adults compared with children is similar to that observed in Singapore.10 Similarly, the age group of late teens to adults (15–39 years of age) was not exempted from severe

**Table 4**

Illness indicators per episode in dengue study cohorts

<table>
<thead>
<tr>
<th>Item</th>
<th>Ambulatory</th>
<th>Hospitalized</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children (n = 8)</td>
<td>Adults (n = 75)</td>
<td>Children (n = 47)</td>
</tr>
<tr>
<td>Days, mean (SD)</td>
<td>5.7 (1.2)</td>
<td>5.4 (1.4)</td>
<td>7.2 (1.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>5.7 (1.2)</td>
<td>5.4 (1.4)</td>
<td>7.2 (1.6)</td>
</tr>
<tr>
<td>Feeling bad or very bad</td>
<td>2.0 (1.4)</td>
<td>3.1 (1.7)</td>
<td>6.7 (2.4)</td>
</tr>
<tr>
<td>Illness</td>
<td>7.4 (1.2)</td>
<td>8.7 (2.3)</td>
<td>12.2 (2.5)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>–</td>
<td>–</td>
<td>3.4 (5.3)</td>
</tr>
<tr>
<td>Healthy days lost equivalents</td>
<td>4.1 (0.9)</td>
<td>4.4 (1.0)</td>
<td>5.7 (1.3)</td>
</tr>
</tbody>
</table>

**Figure 1.** QoL in children (A) and adults (B) over days of illness.
dengue, as shown in outbreaks in Cuba in 1981 and 1997. In some countries such as Thailand or Nicaragua, children are the predominant dengue group.

Compared with ambulatory patients, hospitalized patients had significantly more gastrointestinal symptoms, rendering them at a higher risk of dehydration. Similar findings were observed in a study in Thailand, where approximately 60% of hospitalized children and adults had abdominal pain. In a study in Singapore, loss of appetite, nausea, and vomiting were significantly more common in dengue than non-dengue control patients. On the basis of our findings, clinicians should carefully assess vomiting, diarrhea, and abdominal pain during the febrile stage of disease to determine whether a patient is dehydrated and may require hospitalization. Furthermore, appropriate oral hydration during the early febrile period of the disease could decrease the need for hospitalization, as shown by a study in Nicaragua. Our study also showed that symptoms of the upper respiratory tract infection were common among children and adult dengue patients. Therefore, these symptoms should not be considered as exclusion criteria for dengue. The greater promptness in seeking care among hospitalized patients could be caused by differences in disease presentation, or associations between promptness and the attitudes towards hospitalization of the physicians that they consult.

Thrombocytopenia and clinical evidence of plasma leak were present in 98% and 75% of the hospitalized cohort, respectively, but because of inadequate documentation of bleeding manifestations and tourniquet test, the criteria for WHO classification of DHF was fulfilled in only 53% of children and 40% of adults, compared with 94% and 96%, respectively in Thailand. In Nicaragua, evidence of plasma leakage was present in 30% and 15% of children and adults with dengue, respectively. The mean ± SD duration of fever in our hospitalized cohort was similar to that in Thailand (7.1 ± 1.2 days versus 7.4 ± 2.2 days). The mean duration of illness in the hospitalized cohort in our study of whom 45% were DHF was 12.6 days compared with 10.4 days in Singapore, where the cases were predominantly DF. In our study, despite having more DF cases in the hospitalized cohort, duration of hospitalization (2.8 ± 1.6 days) was the shortest compared with that in Singapore (4.6 ± 1.6 days), Thailand (4.0 ± 1.0 days), and Nicaragua (children = 6.0 days and adults = 5.2 days). This could be caused by different discharge criteria. For example, in our setting, because of bed shortages, patients were usually discharged once stability in hemodynamics and return of appetite were observed, after resolution of fever for approximately 48 hours.

The primary objective of this study was to determine and quantify the impact of symptomatic dengue. Our findings suggest that beyond the life-threatening medical consequences of DHF, dengue is a disease that imposes considerable functional and psychological effects on the afflicted, even in the presumed benign cases. Our study represents the first that examines the QoL serially during the dengue illness episode. Although all patients in this study reported good health before the illness, they were substantially incapacitated by their illness. Apart from the physical discomforts of body aches and pains, approximately two-thirds of patients reported problems with functional and social status of cognition and interpersonal activities, thus contributing to the general perception of a low QoL beginning from the first day of illness and continuing to deteriorate until the third to fifth days. All patients, regardless whether children or adults, ambulatory or hospitalized, showed this trend. Low QoL perception prompting patients to seek early medical attention may have explained this trend. The lowest QoL (35–45 of 100) was observed during the last days of fever and the beginning of the defervescence period. These low QoL values are similar to those reported for chronic conditions such as blindness and below the knee amputation in both legs. Furthermore, the QoL remained low, although improving, after the fever ended, a period when the patient remains vulnerable for complications, such as plasma leakage and bleeding. The visual analog scale used here to estimate QoL has proved to be reliable and generally ranks various health states in the same order as the time-tradeoff and standard gamble approaches, two approaches to estimate quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). Because our study was the first application of the EuroQol thermometer in Malaysia, further validation would be useful. We used the health domains from the WHO World Survey instead of the other items in the EuroQol EQ-5D because we believed the former were more sensitive to dengue. Although each patient reported QoL on multiple occasions, the responses are not necessarily independent observations because patients likely recalled their responses to previous assessments. Because many health domains have been affected during the illness episode, it would be difficult to isolate the role of each factor in the overall low perception of QoL. Presence of plasma leakage was associated with lower QoL in hospitalized children. Among adults, plasma leakage did not affect QoL, which suggested that other undetermined factors could also compromise the QoL of those hospitalized adults without plasma leak. The period of recovery to pre-morbid status was approximately 11–19 days from the beginning of symptoms, being fastest for ambulatory children and adults and hospitalized children with no plasma leakage, and longest for hospitalized adults and children with plasma leakage.

We found less depression and anxiety in children than adults. As each interviewer surveyed both children and adult patients, this finding could not be attributed to interviewer artifacts. When examining hospitalized patients (where the sample was largest), we found that children experienced longer hospital stays than adults and comparable number of domains affected (when not counting affect domains), days of fever, or days feeling bad or very bad. These findings suggest that the children were at least as sick as adults. Thus, the lower rates of depression in children compared with adults could be a result of children being less likely to experience depression or proxies’ limited ability to detect it. The measure of healthy days lost is a first step towards calculating a DALY or QALY effect of dengue. Additional refinements include adjustment from visual analog scales, such as that in the EQ-5D, to time-tradeoff utilities. The prolonged duration of sub-optimal QoL in the young and productive adult population may contribute to the economic impact of dengue.

Although our study site was in a single large urban academic center, the demographic characteristics of our sample resembled both those of a 2002 hospital cohort of clinically diagnosed dengue cases and the national dengue database. The study was limited by the small sample size of ambulatory
pediatric subjects, which made comparison a challenge. Certain clinical features were not routinely elicited by clinicians and small pleural effusions and ascites might have been missed without systematic radiologic imaging, resulting in the underestimation of DHF. Serial blood samples were not obtained and monitoring of temperature was not conducted for ambulatory patients, many of whom received antipyretics. The QoL self-assessments could be biased by the recall for illness days before enrollment and after discharge from hospital or daily follow-ups. However, the lowest QoL was obtained prospectively because it coincided with hospital admissions or clinic visits. Those persons who sought care in this institution might be self-selected or may have been referred by the general practitioner because they felt sicker.

In conclusion, symptomatic dengue, with or without vaso-lopahy, has far-reaching adverse effects involving social function, vitality, and emotional well-being for children and adults. Overall, a dengue episode affects almost every health domain, represents a 60% loss in QoL on its worst days, lasts 9 days (when ambulatory) or 13 days (when hospitalized), which are periods substantially longer than the durations of fever and hospitalization.

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