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ORIGINAL ARTICLE

Dengue and post-infection fatigue: findings from a prospective cohort—the Colombo Dengue Study

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Background: Previous studies on post-infection fatigue in dengue are few but suggest that up to 25% of dengue patients may suffer from fatigue. This study aimed to evaluate the prevalence and associations of post-infection fatigue in dengue patients compared with non-dengue fever patients.

Methods: Post-infection fatigue and its demographic and clinical associations were assessed in adult dengue and non-dengue fever patients 2 months after the acute infection in a prospective cohort study in Sri Lanka. Fatigue at 2 months (primary endpoint) was assessed with the fatigue questionnaire as a dichotomous outcome based on a pre-recommended cut-off (score ≥4) and as the total score from the questionnaire (higher score indicates more fatigue).

Results: Of 260 patients, 158 had dengue and, of these, 51 (32%) had fatigue at 2 months. Risk was higher in dengue patients (vs non-dengue; relative risk [RR] 4.93 [95% confidence interval {CI} 2.3 to 10.4]) and more so in female dengue patients (vs male dengue patients; RR 2.45 [95% CI 1.24 to 4.86]). Severe dengue patients had a higher mean fatigue score (p=0.024).

Conclusions: Post-infection fatigue is an underappreciated burden of this widely prevalent infection. Our findings are useful to triage patients at risk of fatigue for follow-up.

Keywords: Colombo Dengue Study, dengue, fatigue, post-infection fatigue, Sri Lanka

Introduction

Post-viral fatigue is a frequently described clinical phenotype in the medical literature, but the number of prospective studies that have attempted to characterize it using a validated self-report tool are limited.[1–3] Dengue is now arguably the most significant RNA virus infection in humans in terms of annual case incidence (an estimated 390 million cases per year) and the population at risk (an estimated 3.9 billion people), with active disease transmission occurring in 129 countries.[4,5] There is evidence for post-infection fatigue in dengue from a few studies that systematically assessed it[3,6] and from several other studies that use a variety of terms such as asthenia, malaise and weakness to refer to a similar phenomenon months after the acute infection.[7,8] Evaluation of quality of life scores in dengue patients demonstrate that the deterioration of these scores outlasts the duration of fever[9] and may impose a significant burden in terms of lost productivity.[10]

In a prospective study from Singapore,[3] 127 patients hospitalized for dengue fever were interviewed by telephone 2 months after the acute infection with a validated questionnaire to assess fatigue, the Fatigue Questionnaire (FQ).[11] Post-infectious fatigue was found in 31 (25%) patients, but it is uncertain whether the findings are specific to dengue, since the study did not include patients hospitalised with other febrile illnesses. There are several other studies from Brazil, Peru, Cuba, India and Singapore that assessed the persistence of symptoms after recovering from

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acute dengue infection.[7,8,12–17] However, these either do not specifically assess post-infection fatigue or simply assess it as a single question (e.g. Do you have fatigue?) in the medical interview without using a validated tool.

This study aims to systematically evaluate symptoms of post-infection fatigue persisting at 2 months post-infection in dengue patients while comparing the same in non-dengue fever patients. We also aim to identify clinical and demographic associations for post-infection fatigue in dengue.

Materials and methods

The Colombo Dengue Study (CDS) is a prospective observational cohort study conducted at the National Hospital of Sri Lanka (NHSL) by University of Colombo in collaboration with University of New South Wales, Sydney, Australia. A cohort description and an interim analysis of CDS has been published previously.[18] In brief, CDS recruits adult patients with an acute febrile illness for <3 d when clinically suspected as dengue fever (by independent assessment of two medical officers). Patients are recruited from the NHSL, which is the largest public hospital in Sri Lanka. This hospital is in the Colombo district, which has the highest dengue incidence in Sri Lanka.[19] This article refers to patients enrolled into the study from January 2018 to January 2020. Following admission, diagnosis of dengue is confirmed by both an NS1 antigen test at bedside (SD BIOLINE Dengue NS 1 antigen test, Alere San Diego, San Diego, CA, USA) and reverse transcription quantitative polymerase chain reaction (RT-qPCR).[20] The RT-qPCR was carried out as previously described using oligonucleotide primers, dual-labelled probe for dengue virus (DENV) to four serotypes (Life Technologies, Pitam Pura, India) and TaqMan Multiplex Master Mix (catalogue no. 4461881; Applied Biosystems, Waltham, MA, USA) were used for the multiplex RT-qPCR in an ABI 7500 PCR system (Applied Biosystems).

All patients who were admitted on suspicion of dengue fever were managed as such, unless confirmed to have an alternative diagnosis (e.g. typhus, malaria, influenza, leptospirosis) during the hospital stay. After excluding those with an alternative diagnosis, two groups of patients were available to be interviewed at 2 months: confirmed dengue patients (either NS1 test or RT-qPCR was positive) and fever patients with an illness similar to dengue fever but remained undiagnosed (both NS1 test and RT-qPCR were negative for dengue). Children (<18 y of age) and patients with a past psychiatric history were excluded. During the acute infection, all consenting suspected dengue patients were interviewed on admission to hospital and followed up daily from admission to discharge and demographic characteristics, symptoms, laboratory parameters and outcomes (mortality, development of plasma leakage and severe dengue) were recorded. The severity of dengue infection and plasma leakage was documented based on World Health Organization 2009 guidelines on the classification of dengue fever.[21]

Post-infection fatigue was assessed by the FQ,[11] as used by Seet et al.[3] in the previous study from Singapore, 2 months after discharge via a telephone interview of consenting patients (conducted by the same investigator who interviewed the patient during acute infection). This tool has been validated previously for dengue patients in Sri Lanka.[6] The questionnaire consists of 11 items related to physical and mental fatigue. Each item of the questionnaire has four responses (0, none; 1, mild; 2, moderate; 3, severe). A higher score indicates more fatigue and a cut-off ≥4 has been recommended by previous authors[22] when a dichotomous outcome (presence or absence of fatigue) needs to be recorded. We report the results in two subsections corresponding to these two ways of interpreting the FQ (the absolute score and the presence or absence of fatigue). This is because recording a dichotomous outcome alone may not capture the different intensities of symptoms experienced by people.

For an effect size (relative risk [RR]) of 3 between the two groups at a confidence of 0.95 and a power of 80%, the required sample size was 138 per group (in absence of an estimate from previous literature, the incidence of fatigue in non-dengue patients was considered to be at 5%). The presence of fatigue and mean scores of the FQ were compared as dependent variables (in both dengue and non-dengue patients) against patient demographics, symptoms and laboratory investigation results. Furthermore, for dengue patients, the same dependent variables were assessed against the presence of plasma leakage, severe dengue, viral load and infecting serotype. The χ^2 test, independent t test and Mann–Whitney U test were used to explore statistical significances of dichotomous and continuous variables depending on the normality of distributions. Statistical significance was set at $p<0.05$ and was adjusted for multiple comparisons using the Bonferroni correction. When laboratory investigations were compared (as multiple measurements were available for each test), we compared the following parameters: first test value within 3 d of fever (early disease) and highest, lowest and mean value per test throughout the entire hospital stay. All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA).

Results

A total of 260 patients (dengue 158, non-dengue 102) were interviewed at 2 months. Their mean age was 34.3 y (range 14–83, standard deviation 15.3) and 164 (63.3%) were males. A breakdown of patient numbers that were followed up during hospital admission, confirmed to have dengue infection (or not) and then subsequently interviewed is given in Figure 1. The dengue group had more males, a younger age distribution and more clinical symptoms during acute illness compared with the non-dengue patients, as shown in Table 1. A detailed breakdown of patient responses to each component of the FQ is given in Supplementary Table 1.

Associations for the presence or absence of fatigue (as a dichotomous outcome)

When defining post-infection fatigue as a dichotomous outcome based on the cut-off (score ≥4), 60 patients had fatigue. This included 51 (32.3%) dengue patients and 9 (8.8%) non-dengue patients. Dengue patients had a significantly higher risk of fatigue at 2 months after the acute infection (RR 4.93 [95% confidence interval {CI} 2.3 to 10.4], $p<0.001$). Females with dengue infection were more likely to have fatigue than males (RR 2.45 [95% CI 1.24 to 4.86], $p<0.05$). A similar gender-based association

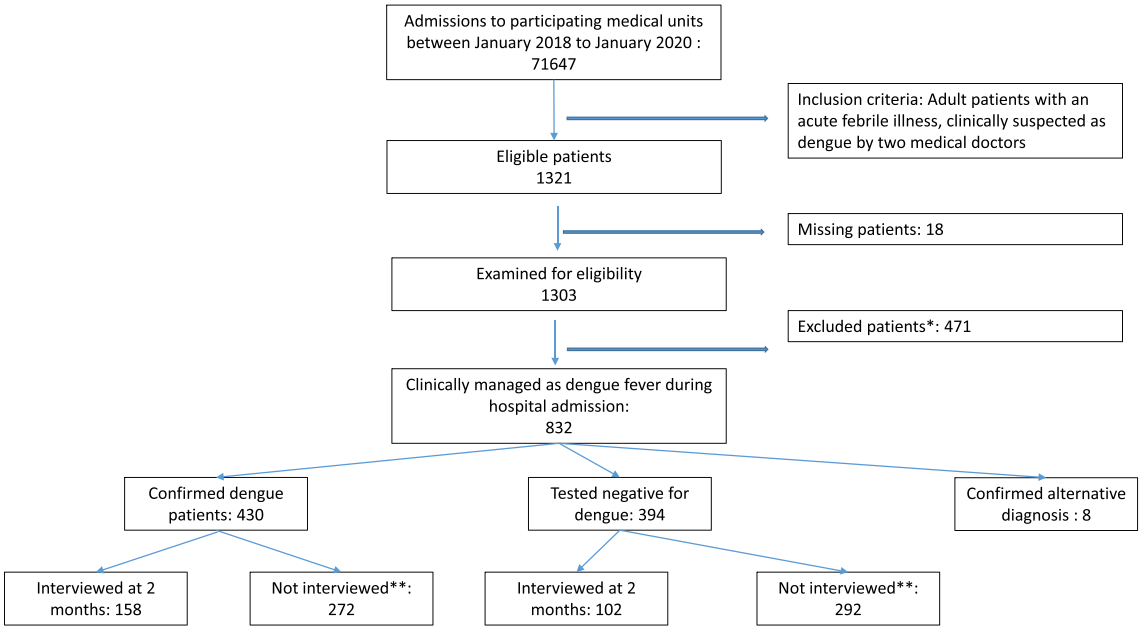

Figure 1. Flow chart of patient recruitment for follow-up interviews at 2 months. *Excluded due to either no consent, age <18 y, self-discharge, admitted with fever for >3 d or already in plasma leakage on admission. **Not interviewed due to no consent (for interviews), past psychiatric illness or not providing contactable phone numbers (two attempts made per person). All interviewed patients were included in the analysis.

for post-infection fatigue was not seen for non-dengue patients (Table 2). None of the clinical features and laboratory parameters assessed had a significant association with the presence of post-infection fatigue in both dengue and non-dengue patients (Tables 3 and 4). There were no associations between minimum, maximum, median and mean values of laboratory parameters assessed throughout the hospital stay and the presence of post-infection fatigue in dengue patients (Supplementary Table 2). In dengue patients, the infecting serotype was known for 132 patients (DENV2: 86; DENV1, 3 and 4: 46), viral load was available for 116 patients, plasma leakage was observed in 45 patients and severe dengue was seen in 10 patients. None of these characteristics were associated with the presence of fatigue 2 months post-infection (Table 5).

Comparison of fatigue scores (as a continuous variable) across different groups

Dengue patients had a significantly higher mean fatigue score compared with non-dengue patients (3.5 vs 0.7; $p<0.001$). The mean difference in fatigue scores for female dengue patients was significantly higher compared with male patients (mean 5.34 vs 2.00; $p<0.001$). A similar difference between genders was not seen between non-dengue patients (mean 1.38 vs 0.43; $p>0.05$). Both dengue and non-dengue patients with diabetes had significantly higher fatigue scores compared with those without diabetes (Supplementary Table 3). There were no significant associations for fatigue scores and the presence or absence of clinical symptoms in dengue and non-dengue patients (Supplementary Table 4). There were also no significant differences in fatigue scores between groups infected with different serotypes (DENV2 vs others) or between those who had plasma leakage and others. However, those who had severe dengue had a significantly higher mean fatigue score than other dengue patients (7.4 vs 3.18; $p=0.024$) (Supplementary Table 5). There was no correlation between viral load and fatigue score (data not shown).

Discussion

This study shows that dengue fever is associated with post-infection fatigue up to 2 months post-infection compared with non-dengue patients with an acute febrile illness. Post-infection fatigue was seen in approximately one-third of dengue patients. Female dengue patients were more likely to meet the definition of fatigue according to the FQ, while those with diabetes or severe dengue were also likely to have a higher score on the FQ compared with others.

Studies on post-infection fatigue in dengue are rare. A recent systematic review that collated evidence from prospective studies assessing fatigue after any acute infection (even when a specific diagnosis was not made) using a validated self-report tool found only 17 eligible studies published by March 2016 across multiple databases (MEDLINE, PsychINFO, Embase).[23] Almost half of these studies (n=9) were on glandular fever, while 3 included any acute infection non-specifically.[23] One study each was on Ross River virus[24] and dengue virus[3] patients. These individual studies attribute various characteristics, such as illness severity, pre-existing psychiatric problems, clinical examination findings (e.g. lymphadenopathy) and perceived levels of stress, to persistent fatigue (assessed 2–6 months after acute infection).[1,3,23–25] The authors of the meta-analysis conclude that risk factors for post–acute infection fatigue can be classified under five recurring themes: biological, social, behavioural, emotional and cognitive.[23]

Table 1. Descriptive statistics of demographic variables and illness-related characteristics of dengue and non-dengue patients

Characteristics	Dengue patients (n=158)	Non-dengue patients (n=102)	p-Value
Demographics			
Male, n (%)	88 (56.1)	76 (74.%)	0.003**
Age (years), median	28	36	0.000**
Pre-existing metabolic comorbidity,[a] n (%)	16 (10.1)	19 (18.6)	NS
Smoker, n (%)	12 (7.6)	10 (9.8)	NS
Alcohol use, n (%)	11 (7.0)	12 (11.8)	NS
Average monthly income (US$), median	188.50	215.42	NS
Clinical symptoms, n (%)			
Headache	110 (69.6)	48 (47.1)	0.000**
Myalgia	106 (67.1)	56 (54.9)	0.048*
Arthralgia	87 (55.1)	41 (40.2)	0.019*
Diarrhoea	29 (18.4)	9 (8.8)	0.034*
Abdominal pain	51 (32.3)	15 (14.7)	0.001**
Dyspnoea	4 (2.5)	1 (1.0)	NS
Vomiting	61 (38.6)	24 (23.5)	0.011*
Retro-orbital pain	20 (12.7)	10 (9.8)	NS
Bleeding	24 (15.2)	5 (5.0)	0.010*
Laboratory investigations, median			
Haemoglobin (g/dL)	13.72	13.9	NS
Haematocrit (%)	40.45	40.65	NS
Platelet count ($\times 10^3/\mu$L)	97.50	129.00	0.0001**
Total leukocyte count ($\times 10^9$/L)	3.68	5.65	0.0000**
Neutrophil count ($\times 10^9$/L)	1.93	2.59	0.0002**
Lymphocyte count ($\times 10^9$/L)	1.22	1.63	0.0003**
Aspartate aminotransferase (U/L)	61.0	39.00	0.0013**
Alanine aminotransferase (U/L)	48.67	36.00	0.0353*
Serum sodium (mmol/L)	136.00	137.00	0.0056*
Serum potassium (mmol/L)	3.70	3.90	0.0323*
Serum creatinine (μmol/L)	67.75	1.30	0.0159*
C-reactive protein (mg/dL)	14.00	14.50	NS
Serum total bilirubin (mg/dL)	8.39	1.20	NS

*Statistically significant with a p-value <0.05.
**Statistically significant with a Bonferroni adjusted p-value <0.013 (demographics), <0.006 (clinical symptoms) or <0.004 (for laboratory investigations).
[a]Includes diabetes mellitus, hypertension, hyperlipidaemia and ischaemic heart disease.
NS: not significant.

The prevalence of post-dengue fatigue (32.3%) in our study is the highest reported in the literature, but the estimate of 25% by Seet et al.[3] in Singapore using the same questionnaire and cut-off is not far behind. Similarly, a smaller, single-centre study in Sri Lanka (which also used the FQ) found 17% of patients (9/52) to have fatigue 1 month after infection.[6] In combination, these results suggest that nearly one-fifth to one-third of dengue patients may suffer from symptoms of post-infection fatigue 1–2 months after infection. This is significant considering that an estimated 96 million symptomatic dengue cases occur every year.

It is not clear how dengue leads to the persistent fatigue. It may be that the complex immunological response (especially in secondary infection) initiated by infection leads to excess cytokine production during the acute phase[26] and the interaction of these cytokines with the neuroendocrine, musculoskeletal and immunological systems might contribute to persistent fatigue.[27] These interactions may also be modulated by host factors such as genetics, sickness, personality traits and vulnerability to psychological stress. However, both our observations and those by Seet et al.[3] indicate that most symptoms and laboratory markers (during acute infection) and having plasma leakage did not predict post-infection fatigue. Notably though, in our study, those with severe dengue had on average a significantly higher score on the FQ compared with other dengue patients, but the size of this subgroup was too small for a definite conclusion. We did not

Table 2. Associations between patient sociodemographic characteristics and presence of fatigue

	Dengue (n=158)			Non-dengue (n=102)		
	Fatigue			Fatigue		
Characteristics	Yes	No	RR (95% CI)	Yes	No	RR (95% CI)
Age (years), median	30.0	27.0	1.02 (1.00 to 1.05)	28.0	36.0	1.00 (0.96 to 1.04)
Gender						
Female	30	39	2.45* (1.24 to 4.86)	3	23	1.52 (0.35 to 6.58)
Male	21	67		6	70	
Pre-existing comorbidity						
Yes	7	9	1.73 (0.61 to 4.95)	4	15	4.16 (1.00 to 17.32)
No	44	98		5	78	
Smoking						
Yes	4	8	1.05 (0.30 to 3.67)	1	9	1.17 (0.13 to 10.42)
No	47	99		8	84	
Alcohol consumption						
Yes	2	9	0.44 (0.09 to 2.14)	1	11	0.93 (0.11 to 8.18)
No	49	98		8	82	

*Statistically significant with a p-value <0.05.

Table 3. Comparison of clinical features of dengue and non-dengue patients with the presence of fatigue

		Dengue			Non-dengue		
Clinical features		Fatigue	No fatigue	OR (95% CI)	Fatigue	No fatigue	OR (95% CI)
Headache	Yes	34	76	0.82 (0.40 to 1.26)	4	44	0.89 (0.22 to 3.53)
	No	17	31		5	49	
Myalgia	Yes	33	73	0.85 (0.42 to 1.73)	3	53	0.38 (0.09 to 1.60)
	No	18	34		6	40	
Arthralgia	Yes	31	56	1.41 (0.72 to 2.78)	3	38	0.72 (0.17 to 3.07)
	No	20	51		6	55	
Diarrhoea	Yes	13	16	1.95 (0.85 to 4.44)	0	9	NA
	No	38	91		9	84	
Abdominal pain	Yes	19	32	1.39 (0.69 to 2.81)	2	13	1.76 (0.33 to 9.41)
	No	49	75		7	80	
Dyspnoea	Yes	2	2	2.14 (0.29 to 15.66)	0	1	NA
	No	49	105		9	92	
Vomiting	Yes	14	47	0.48 (0.23 to 1.00)	3	21	1.71 (0.39 to 7.45)
	No	37	60		6	72	
Retro-orbital pain	Yes	5	15	0.67 (0.23 to 1.95)	1	9	1.17 (0.13 to 10.42)
	No	46	92		8	84	
Bleeding	Yes	10	14	1.62 (0.66 to 3.95)	0	5	NA
	No	41	93		9	88	

NA: not applicable.

Table 4. Comparison of laboratory investigations (within the first 3 d of fever) of dengue and non-dengue patients with the presence of fatigue

	Dengue		Non-dengue	
Laboratory parameter	Fatigue (n=51)	No fatigue (n=107)	Fatigue (n=9)	No fatigue (n=93)
Haemoglobin (g/dL), median	13.3	13.3	13.6	13.6
Haematocrit (%), median	39.4	39.7	41.4	41.5
Platelet count ($\times 10^3/\mu$L), median	126.0	135.0	130.0	137.5
Total leukocyte count ($\times 10^9$/L), median	4.2	4.1	5.2	5.3
Neutrophil count ($\times 10^9$/L), median	2.3	2.9	2.5	3.1
Lymphocyte count ($\times 10^9$/L), median	0.6	0.7	1.1	1.2
Aspartate aminotransferase (U/L), median	50.0	51.5	80.0	45.0
Alanine aminotransferase (U/L), median	34.0	41.5	89.5	36.5
Serum sodium (mmol/L), median	135.0	136.0	141.0	137.0
Serum potassium (mmol/L), median	3.7	3.7	4.4	3.8
Serum creatinine (µmol/L), median	59.0	75.0	41.6	1.3
C-reactive protein (mg/dL), median	13.0	15.5	8.5	14.0
Serum total bilirubin (mg/dL), median	4.9	8.5	7.1	1.1

Table 5. Serotype, plasma leakage and severity of dengue with the presence of fatigue among dengue patients

Variable		Fatigue	No fatigue	RR (95% CI)
Serotype	DENV2	25	61	0.85 (0.39 to 1.83)
	DENV1, 3 and 4	15	31	
Plasma leakage	Yes	19	26	1.85 (0.90 to 3.80)
	No	32	81	
Severe dengue	Yes	6	4	3.43 (0.92 to 12.7)
	No	45	103	

measure cytokine levels during acute admission to correlate with persistent fatigue.

As for associations of post-infection fatigue in dengue, Seet et al.[3] concluded that female gender and older age were significant associations. Other studies on post-dengue fatigue are mostly descriptive and do not explore associations for fatigue.[6,17] Several other prospective studies explore associations for persistent symptoms (not necessarily fatigue) in dengue and if fatigue was assessed, it was only recorded as part of a medical interview without using a dedicated self-report tool.[8,13,16] Yet the association of female gender with persistent symptoms is a recurring finding in several of these studies.[7,8,14,15] The largest of these was a multicentre prospective study from Peru that enrolled 3659 dengue patients and 5408 non-dengue febrile controls to record the persistence of six types of symptoms (respiratory, gastrointestinal, rash, fatigue, headache and body pain) up to 2 months after acute dengue infection. Fatigue in this study was defined as the presence of 'malaise/asthenia' and not by a detailed questionnaire. Interestingly, this study found a higher prevalence of fatigue in non-dengue patients (3.8% vs 2.7%; $p<0.01$), but since a validated tool was not used to assess fatigue, these results are not directly comparable to ours. However, in this study also, females in the dengue group were significantly more likely to report at least one persistent symptom, but not in the control group. The recurrent observation of vulnerability to fatigue in females in both dengue and other conditions (e.g. higher prevalence of chronic fatigue syndrome) have been attributed to hormonal imbalances, reproductive function,[28] genetics[29] and psychosomatic handling of stress[30] or a combination of these. Still, other authors suggest that this discrepancy may be due to males being more reluctant to report symptoms due to cultural or gender norms in some societies. Past psychiatric history (e.g. depression or anxiety disorders) may also influence in self-reporting of fatigue, but in our study anyone with a past psychiatric history was excluded. However, we acknowledge that some people may have undiagnosed psychiatric comorbidities and it is also difficult to adjust for personality traits influencing the role of sickness. While the exact reason for the higher incidence of post-dengue fatigue in females cannot be resolved by an epidemiological cohort study such as ours, the recurrent association of females having either fatigue or persistent symptoms after an acute illness should alert clinicians to arrange a follow-up visit. It should also alert researchers and policy planners to consider evaluating the economic impact of post-dengue fatigue (days

lost to work or school) to minimize a neglected part of the dengue disease burden. A recent modelling of economic burden due to persistent dengue symptoms in Mexico estimated an additional cost of approximately US$22.6 million per year,[10] which is not trivial.

This study has several limitations. The most notable is that a definite diagnosis was not made for patients in the non-dengue group. However, making a diagnosis is not considered cost effective for patients who often recover from a viral flu-like illness and they were symptomatically managed as for dengue until discharge. Making a diagnosis in this context is for academic interest only, as it usually does not alter patient management. However, if patients were clinically suspected of having an alternative diagnosis (e.g. malaria, leptospirosis), specific diagnostic tests were carried out and those with a confirmed alternative diagnosis were excluded from this study. As for other limitations, the definition of fatigue in this study as determined by the FQ was entirely subjective and based on self-reports, which may be biased by pre-existing sickness and personality traits. As highlighted in Table 1, there were some significant differences at baseline between the dengue group and non-dengue group and hence caution must be exercised in interpretations when these two groups are compared against each other. For example, although we can confirm that females with dengue were at higher risk of having fatigue compared with males with dengue, we cannot confirm the results of the same analysis for the non-dengue group (which showed no association between genders), given the small number of females in that group. We also cannot confirm that the higher risk of females having fatigue is unique to dengue fever, as the non-dengue 'control' group had fewer females. The control group was smaller than the expected sample size because some patients had to be excluded after an alternative diagnosis was confirmed and more in this group refused consent to be interviewed at 2 months. Similarly, in the serotype analysis, most infections were of DENV2, so all other serotypes had to be combined into a single group to compare with DENV2. Finally, this cohort is from a single centre in Sri Lanka that excluded patients <18 y of age. The lack of heterogeneity in some confounders (sociodemographic variables, cultural variables, younger age groups), limits the generalizability of our results. Yet it highlights the fact that this phenomenon needs to be explored globally to understand its true impact.

In conclusion, up to one-third of dengue patients may be have post-infection fatigue, with a higher risk in females. From a clinical perspective, these patients may benefit from a follow-up visit to discuss their adjustment to activities of daily living, study and work. However, arranging follow-up for all patients during epidemics may be impractical and therefore developing a triaging system to recall patients based on risk associations as identified in this and other similar studies would be a more feasible approach. Alternatively, patient education at discharge on post-infection fatigue in dengue will help those needing further assistance to seek medical advice. From a research perspective, more studies in different countries are required to systematically evaluate post-infection fatigue in dengue to identify the role of confounders and associations that may influence its impact.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: PCS, SR, PW, CR and SDF conceptualized the study. PCS did the patient interviews, data analysis (with contributions from PW and NLdS) and writing of the first draft under the supervision of SDF and CR. LG and GNM provided laboratory supervision and support for dengue serotyping. CR and SDF shared equal supervisory responsibilities for the project. All authors revised and approved the final version of the manuscript. CR and SDF contributed equally to this work.

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Ethics approval: Ethics approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo (EC/17/080) and the Ethics Review Committee, NHSL (ETH/COM/2017/12). Written consent was obtained from the copyright holders to use the Fatigue Questionnaire. Written informed consent was obtained from all the participants before their recruitment for the study.

Data availability: The data presented in this article can be shared upon reasonable request to the corresponding author. Details that may lead to identification of individual patients will not be made available.

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