Depression and anxiety among pediatric and adult in-patients with dengue fever in Metro Manila, Philippines

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ABSTRACT

Background: Psychiatric symptoms have been reported in adult patients with dengue fever (DF); however, information on pediatric patients remains inadequate. We sought to identify the prevalence and determinants of depression and anxiety and identify other encephalopathy symptoms among pediatric and adult patients with DF.

Methods: This cross-sectional study used a non-probability purposive sampling method among clinically or serologically confirmed in-patients with DF. Participants completed the Revised Child Anxiety and Depression Scale for pediatric patients and youth controls and Hospital Anxiety and Depression Scale for adult patients.

Results: The prevalence of depression and anxiety were significantly higher among 225 pediatric patients than among 81 youth controls, but was lower than that among 43 adult patients. A multiple linear regression analysis of socio-demographic and clinical data found that age, family history of DF, ≤ 2 days of hospitalization, and myalgia and arthralgia tended to increase depression and anxiety scores of pediatric patients. Further, 26.7% of pediatric patients reported irritability, agitation, visual hallucinations and aggressiveness.

Conclusion: Prevalence and determinants of depression and anxiety and the presence of encephalopathy symptoms differ between pediatric and adult patients. Longitudinal post-DF recovery studies should be conducted to examine whether these symptoms may develop to subsequent chronic psychiatric conditions in the future.

Keywords:

Anxiety, depression, dengue fever, pediatric psychiatry, encephalopathy

Background

As the world's most rapidly spreading mosquito-borne disease, dengue fever (DF) causes approximately 50 million cases a year, putting an estimated 2.5 billion people at risk, especially children [1]. Its incidence has increased by 30 times in the last five decades [2], and is now prevalent in 128 countries [3]. It presents flu-like symptoms that include high-grade fever accompanied by headache, myalgia and arthralgia, nausea and vomiting, intense abdominal pain, rash, retro-/peri-orbital pain, bleeding and low platelet count (thrombocytopenia), which can lead to acute organ failure, cardiomyopathy, encephalitis, profound shock and death [1]. Recently, the number of studies reporting this virus to be neurovirulent has increased [4], associating it with neurological complications in patients with DF [5].

The most prevalent neurological disorder occurring during DF is encephalopathy [6]. However, information on pediatric patients seems inadequate compared with that on adult patients. Adult patients with DF exhibit mood disorder with manic features [7], psychosis [8], mania [9, 10], depression and anxiety [11-14]. The prevalence of borderline and clinical depression and anxiety among adult patients with DF ranges from 60% to 81% [12, 13]. During the acute phase, majority (90%) of the patients exhibit thanatophobia or fear of death (90%), and during the recovery phase (1 week after onset of DF), more than half (55%) of patients develop fear of mosquitoes (55%) [11, 14]. Most importantly, the severity of DF symptoms such as fever, headache, myalgia, arthralgia, retro-/peri-orbital pain and thrombocytopenia positively correlates with depression and anxiety [12].

Depression and anxiety have been investigated in children with fatigue syndrome, fibromyalgia, migraine/tension headache [15], chronic abdominal pain [16], juvenile idiopathic arthritis [17], cancer [18], and HIV [19], yet information among pediatric patients with DF remain inadequate. One prospective study provides information on neurologic manifestations of DF in children. Pancharoen and Thisyakorn [20] reported that 80 of 1,493 (5.4%) Thai in-patient children (3 months to 14 years old), who had serologically confirmed DF diagnosis, exhibited seizure and encephalopathy-like depressed sensorium and mental confusion during the febrile (acute) stage of DF based on recorded medical charts. However, studies that prospectively used self-report screening tool to detect depressive and anxiety symptoms [21]; which has a high acceptance and response rate (99%) and a low refusal rate (1%) among in- and out-patients [22], are lacking. To date, the study done by Mushtaq and

Zahir [23] is the only one known study, to our knowledge, that has used self-report screening tool to measure depression, anxiety and stress and investigated its relationship with self-efficacy including pediatric patients with DF. The study used Depression Anxiety and Stress Scale (DASS) to measure depression, anxiety and stress and General Self-Efficacy Scale (GSES) to measure self-efficacy among the participants. They found out that self-efficacy has negative correlation with depression, anxiety and stress, thus, developing self-efficacy among the patients is deemed necessary. Although this study adds to the emerging topics on the presence of depressive and anxiety symptoms among pediatric patients with DF, there is still a pressing need to conduct more studies to measure the impact of DF infection on mental health of pediatric patients.

Therefore, this study aimed to estimate the prevalence of depression and anxiety among adult and pediatric in-patients with DF and compare it with that among non-patient youth controls. We also sought to comparatively explore the determinants of depression and anxiety by socio-demographic profiles, clinical parameters and clinical symptoms and to identify other encephalopathy symptoms that occur during the infection. We hypothesized that the prevalence of depression or anxiety among pediatric patients with DF would be higher than that among youth controls, and determinants would include pain-related DF symptoms including headache, myalgia, arthralgia, retro-/peri-orbital pain and abdominal pain.

Methods

Study and sampling design

This cross-sectional study involved in-patients with DF at three public tertiary (>100 beds) hospitals in Metro Manila, Philippines: San Lazaro Hospital, a referral facility for infectious/ communicable diseases; Quezon City General Hospital and Pasay City General Hospital and school-based youth controls during the DF peak transmission from 26th July 2017 to 26th November 2017. The patients with DF and youth controls were purposively selected based on the pre-determined inclusion and exclusion criteria, availability, willingness to communicate their experiences and participate in the study [24-26]. A sample size of 355 was recommended to detect any degree of depression and anxiety in 50% of patients with DF, with a 5% margin of error, 95% confidence level ($\alpha = 0.05$; critical value/Z-score of 1.96) based on 4, 525 cases in Metro Manila, Philippines,

during the same period in 2016 [27]. Metro Manila had an increased number of DF cases by 15.5% from 1st January to 6th May (morbidity week, 1–18), which was one of the highest rates in the country in 2017 [28].

Participant inclusion and exclusion criteria

A bedside interview was conducted among in-patients with serologically (laboratory) confirmed or clinically diagnosed with DF. Patients were grouped based on age criteria of screening tools, pediatric patients (age 8–17 years) and adult patients (age >17 years). Youth controls were school-based samples who were selected based on age (8–17 years), grade level (Grade 3–10) and sex with no current or existing symptoms or diagnosis of DF. Pediatric and adult patients with DF, and youth controls who were recruited had no history and/or existing diagnosis of psychiatric and/or medical condition for which they had received medical advice or treatment prior to the interview. Patients with life-threatening comorbidities and youth controls who were not able to comply with consent procedures were excluded.

Ethical considerations and procedures

Our study was approved by the Research Ethics and Review Unit of San Lazaro Hospital, Research Ethics and Technical Committee of Pasay City General Hospital and Planning, Development, Education and Research office of Quezon City General Hospital. It was written and conducted in accordance with the Declaration of Helsinki [29], ICH-GCP Guidelines [30] and National Ethical Guidelines for Health Research [31]. Initially, informed consent was obtained from all the patients and their parents, legally authorized representatives (LARs) or caregivers, especially for those who were under 18 years of age. They were asked to read and sign an informed consent form in Filipino before their participation in the study. Patients (age 15–18 years) co-signed the informed consent forms with a parent, LAR or caregiver. Verbal assent was accepted for children aged 7–12 years, whereas an assent form was signed by children aged 12–15 years, with solicited informed consent from their parent, LAR, or caregiver. Interviews were rescheduled for patients who could not participate due to sickness and severity of symptoms (e.g. intensive care unit confinement for severe dengue patients). In some cases, a parent, LAR, or caregiver was asked to complete the forms and a Revised Child Anxiety and Depression Scale (RCADS)-Parent version for pediatric patients (aged 8–17 years). Recruitment and interviews of patients were completed by one trained investigator who was supervised by physicians, nurses and co-investigators assigned at each hospital while the youth controls were recruited and interviewed by guidance and counseling

personnel and a psychologist based on the inclusion and exclusion criteria. To avoid bias, interviews were done with a consistent pre-determined instructions and questions using structured forms and standardized self-report screening tools. This was done to expect a fairly consistent data from one participant to another. The investigator and interviewers reviewed participants' answers for missing responses to achieve a 100% completion rate. Forms and screening tools were coded based from a unique numerical assignment given to each patient (P001-P364) and youth control (C001-C081) for their protection and privacy. Participants were informed about their scores on the tests, and a consent for further psychiatric assessment was solicited from those whose scores suggested a need for clinical intervention during follow-up.

Forms and Measures

Socio-demographic Profile, Clinical Parameters and Symptoms: Socio-demographic profile included age, civil status, gender, educational attainment, occupation, family's monthly income and living arrangements. Clinical parameters, including admitting diagnosis information, patient and family history of DF, serologic test results (NS1Ag or BLOT: IgG, IgM) and laboratory data (*i.e.* complete blood count with platelet count), were obtained from medical charts. The inclusion of family DF history was to investigate whether a previous diagnosis or history of DF in a family would be associated with an increased depression and anxiety scores among the patients with DF. Clinical DF diagnosis were made under the following circumstances in three categories: probable (lived or traveled to endemic areas, has fever and two DF symptoms), dengue hemorrhagic fever (DHF) with or without warning signs (abdominal pain, vomiting, mucosal bleeding, lethargy, liver enlargement [$>2\text{cm}$], decreased platelet count or thrombocytopenia) and severe dengue (severe plasma leakage, hemorrhage, and organ impairment) [1]. These were used to identify the patient's current dengue infection phase (acute, febrile–critical and recovery phase). Acute phase is the onset of high-grade fever and other warning signs (e.g. headache, myalgia, arthralgia, nausea and vomiting, mucosal bleeding and thrombocytopenia) usually lasting for a week. Some patients may develop rashes, signaling the beginning of the recovery phase [1]. During this phase, well-being improves, some warning signs tend to abate and platelet count typically starts to rise [1]. Clinical symptoms or warning signs were also queried.

The Revised Child Anxiety and Depression Scale (RCADS): RCADS-25 is a shorter version of the RCADS-47 developed by Chorpita et al. [32], having child and parent versions [33]. The child version was administered to

pediatric patients and youth controls, whereas the parent version was administered to parents of pediatric patients who could not complete the child version due to sickness. RCADS-25 has two scales as follows: depression (10 items) and anxiety (15 items). Items were rated on a 4-point Likert-scale from 0 (“never”) to 3 (“always”) and were scored and interpreted using a “t-score.” T-scores are transformed raw scores used to obtain a normal distribution with a maximum score of 80. A t-score of 65 means borderline and a t-score of 70 means clinical threshold [33]. Both scales have good internal consistency (Cronbach’s alpha) of $\alpha = 0.78$ and $\alpha = 0.88$ in clinical and general or school-based populations [32-34]. This tool has been reported to be a cross-culturally reliable measure of depressive and anxiety symptoms for children and adolescents [35]. A detailed information on permission acquisition, translation and validation procedures of the Revised Child Anxiety and Depression Scale-25 (RCADS-25) is provided as Additional file 1.

The Hospital Anxiety and Depression Scale (HADS): Adult patients (aged >17 years) completed the HADS-P, the validated Filipino language version of the HADS [21], which is a reliable and valid screening tool developed by Zigmond and Snaith [36] for identifying anxiety and depression. HADS/HADS-P is a 14-item self-assessment screening tool answered on 4-point (0–3) rating scale; its subscales are interpreted in ranges: normal (0–7 points), borderline or suggestive of the presence of either anxiety or depression (8–10 points) and clinical or probable presence of mood disorder (≥ 11 points) [36]. Further information on permission acquisition of the Hospital Anxiety and Depression Scale (HADS) is provided as Additional file 2.

Encephalopathy Symptoms: Patients and their parents/guardians were asked to report other encephalopathy symptoms observed during the onset of disease and hospitalization. Moreover, a Yes-or-No question was asked to identify fear of mosquitoes, along with seven follow-up questions based on diagnostic criteria of Specific Phobia in the *Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV-TR)* 300.29 [37]. Answers on encephalopathy symptoms were translated into English by an independent bilingual translator and were analyzed using content analysis, a method that can identify patterns across qualitative data (words or phrases) that can be counted (frequency) for quantitative analyses [38-40].

Statistical and Data Analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences version 25 (IBM Corp., Armonk, NY, USA). An independent t-test was conducted to test the significant differences in the mean depression and anxiety scores (t-scores) between pediatric patients and youth controls. Chi-square test was used to test the significant difference in the prevalence (%) of pediatric and adult patients and youth controls with depression and anxiety. Odds ratio effect sizes were also computed to measure the differences in the proportion of those with depression and anxiety among pediatric and adult patients and youth controls. Multiple linear regression was conducted by inputting all variables (dummy variables [i.e. 0 or 1] for categorical variables) in the model using a stepwise method in forward selection to identify significant ($P < 0.05$) determinants of depression and anxiety. We quantified the prevalence (%) of patients' fear of mosquitoes, and encephalopathy symptoms were analyzed using content analysis.

Results

Socio-demographic profile, clinical parameters and symptoms

Initially, 445 participants (patients, 364; youth controls, 81) were recruited in the study, but only 268 patients with DF were found eligible for interview and testing based on age requirements of the screening tools (age, <7 years). Data from 349 participants, comprising 81 youth controls, 225 pediatric patients and 43 adult in-patients with DF, were included in the analysis. The youth controls, male ($n = 41$) and female ($n = 40$), had a mean (M) age of 11.5 and standard deviation (SD) ($\pm$) of 2.23 years. Pediatric patients had a mean age of 10.96 (± 2.95) years, 53% were males and 83.4% belonged to a family with a monthly income of $\leq 10,000$ pesos. The age of adult patients ranged from 18 to 49 years (M , 22.81 ± 8.54), 60.5% were males, 81.4% were single, 42.1% were employed and 69.8% had a monthly family income of $\leq 10,000$ pesos. Three-fourths of pediatric (76.4%) and majority of adult patients (97.7%) had DHF with warning signs. During the interview, majority of pediatric patients (79.6%) and adult patients (76.7%) were in the acute (febrile–critical) phase of DF. Thrombocytopenia and rashes were the most commonly reported symptoms among pediatric (67.8% had $\leq 9,900/\text{mm}^3$ platelet count and 42.7% had rashes) and adult patients (83.3% had $\leq 9,900/\text{mm}^3$ platelet count and 41.4% had rashes). More detailed information on the socio-demographic profile, clinical parameters and clinical symptoms of pediatric and adult patients is provided as Additional file 3.

Prevalence of depression and anxiety

There was no significant difference between the prevalence of depression among youth controls (13.3%) and pediatric patients (8.6%); however, pediatric patients (34.2%) had a significantly ($P < 0.05$) higher prevalence of anxiety than the youth controls (19.8%) as shown in **Figure 1**. This represents the fact that based on the odds ratio, pediatric patients were 1.6 times more likely to be depressed and 2.1 times more likely to be anxious than youth controls. Further, a significantly larger proportion of adult patients had depression (27.9%) and anxiety (88.4%) than pediatric patients. Adult patients with DF were 2.5 times more likely to have depression and 14.6 times more likely to have anxiety than pediatric patients with DF. Moreover, based on the odds ratio, adult patients with DF were 4.1 times more likely to be depressed and 30.9 times more likely to have anxiety symptoms than youth controls. Pediatric patients had significantly higher mean depression (52.29 ± 9.86) and anxiety (59.33 ± 11.48) scores than youth controls (49.65 ± 10.37 and 56.39 ± 10.01 , respectively) as shown in **Figure 2**.

Determinants of depression and anxiety

The multiple linear regression analysis (**Table 1**) showed that the presence of myalgias and arthralgias and having a family history of DF tended to increase depression scores, whereas ≤ 2 days of hospitalization and age (older) both increased anxiety scores among pediatric patients with DF. Among adult patients with DF, being male tend to have increased depression, whereas DHF with warning signs and retro-/peri-orbital pain both decreased the depression scores. Lastly, the presence of fever and a positive NS1Ag result both increased anxiety scores among adult patients with DF.

Self/Parent-reported Encephalopathy Symptoms

In total, 38 (16.9%) pediatric patients and 11 (25.6%) adult patients reported fear of mosquitoes. However, the reports of fear of mosquitoes were not sufficiently intense to qualify for an anxiety disorder or phobia. Moreover, encephalopathy symptoms were reported among 60 (26.7%) pediatric patients and 8 (18.6%) adult patients, wherein odds ratio showed that pediatric patients with DF were two times more likely to report encephalopathy symptoms than adult patients with DF. Additionally, 26 (52.9%) pediatric patients and 5 (7.3%) adult patients with encephalopathy symptoms reported irritable mood or irritability, and 13.2% of pediatric patients and 1.47%

of adult patients reported agitation. Visual hallucinations (5.9%) and aggressiveness (5.9%) were reported only among pediatric patients during the onset of dengue infection. The table showing the results of content analysis on the reported fear of mosquitoes and encephalopathy symptoms is provided as Additional file 4.

Table 1 Determinants of depression and anxiety among pediatric and adult patients with DF

Outcome Variables		Determinants		Determinant		Model
			R ²	β	p-value	p-value
Depression	Pediatric	Myalgias and arthralgias	0.07	4.87	0.002	<0.001
		Family history of DF		3.19	0.028	
	Adults	Absence of retro-/peri-orbital pain	0.31	-3.60	0.002	0.002
		Gender (male)		1.43	0.042	
		Diagnosis (DHF w/ warning signs)		-3.39	0.043	
Anxiety	Pediatric	Age	0.15	1.26	<0.001	<0.001
		Days in the hospital (≤2 days)		1.26	0.005	
	Adults	+NS1Ag	0.29	2.41	0.002	0.001
		Fever		3.06	0.017	

β = Beta coefficients; DHF = Dengue Hemorrhagic Fever; DF = Dengue Fever; (+) = positive; NS1Ag = Non-Structural protein

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Discussion

Results support our hypothesis that the prevalence of depression and anxiety among pediatric patients with DF would be higher than that among youth controls and is determined by pain-related DF symptoms like myalgias and arthralgias. The symptoms of pain related to myalgias and arthralgias are results of inflammatory cytokines, such as interleukin 1 beta (IL-1 β), interleukin 2 (IL-2) and interleukin 6 (IL-6) [41]. These cytokines were found to be of significantly higher levels among children and adolescents with major depressive disorder (MDD) compared with healthy youth controls [42-45]. Another determinant which also increased depressive mood and anxiety symptoms among pediatric patients was ≤2 days of hospitalization. High depressive and anxiety symptoms during the ≤2 days of hospitalization would have been aggravated by the pediatric patients' fear of medical settings and receiving of medical care as common symptoms of anxiety [46]. Children usually report

medical procedures, such as drawing of blood, as traumatic and medical professionals, such as doctors and nurses, as inflictors of trauma [47]. Further, family history of DF also tended to increase depression among pediatric patients with DF. An indicator of anxiety disorders in children is worrying about multiple issues like future events [48], for instance, contracting dengue. This can be linked to a painful past experience, such as a family member being hospitalized due to the disease. Observing how symptoms can be severe and serious and the level of associated pain may have affected their perception of the disease and their response: being depressed. These fears and the pain associated with myalgia and arthralgia during the ≤ 2 days of hospitalization may have aggravated higher depression and anxiety symptoms among pediatric patients compared with the youth controls.

The lower prevalence of depression and anxiety in pediatric patients than in adult patients could be explained by the assumption that the presentation of depression and anxiety may significantly differ between children and adults [32]. In children, depression and anxiety increases with age [49], and children present with sadness through observable behaviors instead of language [50]. Although parents can help evaluate children's depressive and anxiety symptoms as recommended by clinicians [51], this presents another potential reason for the low prevalence of depression and anxiety in pediatric patients. Compared with their parents, children report more depressive symptoms because parents tend to be insensitive to a child's depressive symptomatology [52]. Another reason could be the lesser ability of pediatric patients to correctly understand the meaning of their disease and clinical terminologies; it has been reported that children and adolescents with chronic illnesses have limited knowledge of their conditions and perceive their diseases differently from adults [53, 54].

The results confirm that pediatric patients with DF also exhibit depressive and anxiety symptoms during DF infection. However, we also found out that 26.7% of pediatric patients with DF, compared to 18.6% of adult patients with DF, reported encephalopathy symptoms, such as irritable mood/irritability, visual hallucination, agitation and aggressiveness. Children are more likely to be irritable and agitated and are most likely to report possible delusions or hallucinations which are symptoms of MDD [46, 55], than older patients. Irritability which is an overlapping symptom among children and adolescents [48], is also a diagnostic criterion for anxiety disorder, for MDD and for disruptive mood dysregulation disorder of the new DSM-V and oppositional defiant disorder of the International Classification of Disorders (ICD-11) among children [56]. Further, one of the

encephalopathy symptoms unique to pediatric patients with DF was visual hallucination. Hallucinations are key features of psychotic conditions and acute neurological states, such as encephalitis, and are often presented with delirium and delusions which are more prevalent in children than adults [57]. This confirms that they are also prone to exhibit encephalopathies like adult patients with DF, who were reported in previous studies of having auditory and visual hallucinations, agitation and delusional fears, irritable affect or behavior, persecutory delusions and psychotic episodes during dengue infection [58, 8]. However, information on whether these encephalopathies, more so, the depressive and anxiety symptoms are present only during the infection and may disappear on its own or may persist after the infection, is unknown. Thus, longitudinal post DF recovery studies would provide information on the possibilities that these symptoms may or may not develop to subsequent chronic psychiatric conditions in the future.

Although age- and pain-related symptoms during ≤ 2 days of hospitalization increased depressive mood and anxiety symptoms among pediatric patients with DF, clinical parameters and clinical symptoms tended to increase depression and anxiety among adult patients with DF. Pro-inflammatory cytokines seem to be a common factor in the preponderance of clinical parameters, such as higher rates of positive NS1Ag during the acute phase of DF and symptoms of fever and thrombocytopenia among adult patients with DF. There is a high rate of non-structural protein (NS1) in the bodies of patients with DF during the acute phase increases serum levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha and IL-6 [59, 60]. The production of high serum levels of these cytokines is associated with depression [61], major depressive disorder (MDD) [62] and anxiety symptoms [63]. Moreover, these cytokines have endogenous pyrogenic properties that cause fever and can also decrease brain-derived neurotrophic factors (BDNF) [64, 65]. Low serum level of BDNF, sourced from platelets, has been found in patients with MDD, and increased levels have been found to be associated with antidepressants [66]. To our knowledge, there has been no known study which reported direct associations between serologic test results specifically presence of positive NS1 antigen and immunoglobulin M and G antibodies and different psychiatric manifestations. Thus, we recommend future studies to focus on dengue patients with serologically confirmed dengue diagnoses to emphasize the raw and clear association between the infection and psychiatric manifestations and would later on encourage studies to test this hypothesis at the molecular level (e.g. serologic test results and the presence of NS1Ag and psychosis).

Another interesting, yet unexpected finding was the emergence of DHF with warning signs and presence of retro-/peri-orbital pain decreasing depression among adult patients with DF. These results can be explained by the fact that majority of adult patients had DHF with warning signs diagnosis (97.6%) and had no retro-/peri-orbital pain (88.4%). Thus, there was higher tendency for those adult patients who had probable diagnosis (2.3%) and had retro-/peri-orbital pain (11.6%) to have lower depression scores. Being male also tend to increase depression among adult patients with DF. However, the high number of male adult patients may have resulted in a potential bias because female patients were under-represented in this study. In general, the low number of adult patients with DF was also seen to be a limitation in this study. This may have been caused by the reason that only those adult patients who reported severe symptoms and those who needed special attention were admitted to hospital and others were asked to stay at home and consult outpatient clinics which limits the prevalence of psychiatric manifestations in this infection to those admitted to hospitals. Therefore, we recommend that future studies also include out-patients to see whether hospitalization is confounding the association between the constructs and dengue infection.

The low consent rate (<1%) for referral to further psychiatric assessment to assess the false positive and negative responses of the patients in the structured tools, for example, HADS [67] has highlighted how patients view mental health disorders. This may have been affected by cultural orientation and perception of depression and anxiety and treatment-seeking response among patients with DF in this study. In the Philippines for example, as a collectivist-oriented culture [68], with greater social support and where family and wider society are more highly considered than own self, a lower tendency to develop depressive disorders can be expected [69]. Moreover, many cultures view mood disorders as a social and moral problem associated with stigma and loss of reputation, not as mental health problems [70]. These conditions are perceived as a moral or character development that requires self-mastery and endurance and help or treatment with medication is seen as unnecessary [71].

To our knowledge, this study is one of the very few reports on psychiatric manifestations in patients with DF, more so, among pediatric patients with DF. However, whether the findings are generalizable or not, remains unknown and we consider income, hospital setting and time as potential threats to external validity of the study findings. Participating hospitals were public tertiary hospitals which limits the study findings to low-income

families, thus, future studies may include patients admitted in private hospitals to see whether hospital setting is confounding the relationship between the infection and the constructs. Moreover, association of income with the constructs was also hard to estimate. Future studies may consider to address this issue by including patients with average to high monthly family income and match them with controls. Lastly, this study is limited only to DF cases during the peak transmission or rainy seasons from July to November. Thus, the results that patients with DF had high depressive and anxiety symptoms during this time may not apply to other periods where there is low transmission of DF. Thus, future studies may rely in comparing patients interviewed during the high transmission season and patients interviewed during low transmission season in order to investigate whether results collected may be generalizable in any period of time. Most importantly, although this study provides benchmark information on the depressive, anxiety and encephalopathy symptoms among pediatric patients with DF, studies remain inadequate. More so, determining whether the findings may only be specific to pediatric patients with DF or may be extended to children with other serious infections in general, also remains unknown, thus, needs to be studied.

With a 100% participation rate among patients with DF, this study was able to include a relatively large number of pediatric patients with DF, which was considered as its main strength. The study was also able to estimate the prevalence of depression and anxiety among pediatric patients with DF and compared it with youth controls and adult patients with DF with the use of standardized self-report screening tools. Moreover, the study also utilized structured interview in collecting information on the presence of encephalopathy symptoms during the infection. Thus, the combination of these quantitative and qualitative techniques was also considered as one of the strengths of this study. Furthermore, the inclusion of clinical data (e.g. DF history, serologic test results, DF symptoms) was also able to provide information on the determinants of high anxiety and depressive symptoms among pediatric and adult patients with DF. The inclusion of youth controls as reference in comparing the prevalence of depression and anxiety among pediatric patients could also be one of this study's main strengths. However, the study failed to include equal number of youth controls with pediatric patients with DF which therefore decreased the ability of the study to draw generalizable conclusions from the findings. Thus, we recommend that future studies may consider doing a complete matching of pediatric patients with DF and youth controls by age and sex.

Conclusion

In this study, we compared the prevalence and determinants of depression and anxiety between pediatric and youth controls and pediatric and adult patients with DF through the use of a self-report questionnaire. We found that pediatric patients had significantly higher mean depression (52.29 ± 9.86) and anxiety (59.33 ± 11.48) scores than youth controls (49.65 ± 10.37 and 56.39 ± 10.01 , respectively). There was also a significantly higher prevalence of depression (27.9% vs. 13.3%; $P < 0.05$) and anxiety (88.4% vs. 34.7%; $P < 0.001$) among adult patients than among pediatric patients, indicating that adult patients with DF were 2.6 times more likely to have depression and 14.3 times more likely to have anxiety than pediatric patients with DF. Depression and anxiety symptoms tend to increase with age (older) and presence of pain-related symptoms (myalgia and arthralgia and family history of DF) during ≤ 2 days of hospitalization among pediatric patients. Fever and clinical parameters (positive NS1Ag results) determined depressive and anxiety symptoms among adult patients with DF. Although the prevalence of depression and anxiety was higher among adult patients, 60 (26.7%) pediatric patients reported encephalopathy symptoms, such as irritable mood/irritability, visual hallucination, aggressiveness and agitation during the onset of DF. This implies that patients with DF, especially pediatric patients are prone to exhibiting encephalopathy like adult patients with DF. However, information on whether these encephalopathies, more so, the depressive and anxiety symptoms are present only during the infection and may disappear on its own or may still persist after the infection, is unknown. Thus, longitudinal post DF recovery studies would provide information on the possibilities that these symptoms may or may not develop to subsequent chronic psychiatric conditions in the future.

Abbreviations

DF, Dengue fever; ICH-GCP, International Conference on Harmonization-Good Clinical Practice; LARs, Legally authorized representatives; RCADS, Revised Child Anxiety and Depression Scale; NS1Ag, Non-structural protein 1 antigen; IgG, Immunoglobulin G; IgM, Immunoglobulin M; HADS, Hospital Anxiety and Depression Scale; DSM, Diagnostic and statistical manual of mental disorders; DHF, Dengue hemorrhagic fever; IL-1 β , interleukin 1 beta; IL-2, interleukin 2; IL-6, interleukin 6; MDD, major depressive disorder; BDNF, brain-derived neurotrophic factor; ICD, International Classification of Disorders.

415 **Declarations**

416 **Ethics approval and consent to participate**

417 This study was approved by the Research Ethics and Review Unit of San Lazaro Hospital, Research Ethics and
418 Technical Committee of Pasay City General Hospital and Planning, Development, Education and Research office
419 of Quezon City General Hospital. Informed consent was obtained from all the patients and their parents, legally
420 authorized representatives (LARs) or caregivers, especially for those who were under 18 years of age.

421

422 **Consent for publication**

423 Not applicable.

424

425 **Availability of data and materials**

426 The datasets supporting the conclusions of this article are included within the article and its additional files.

427 MS_DADF_AF1.docx Additional file 1: Detailed description of permission acquisition, translation and validation
428 procedures of the RCADS-25. (DOCX 14 KB)

429 MS_DADF_AF2.docx Additional file 2: Further information on permission acquisition of the HADS. (DOCX 13 KB)

430 MS_DADF_AF3.ver.2.docx Additional file 3. More detailed information on the profile of pediatric and adult
431 patients with DF. (DOCX 25 KB)

432 MS_DADF_AF4.docx Additional file 4: Results of content analysis on the reported fear of mosquitoes and
433 encephalopathy symptoms. (DOCX 18 KB)

434

435 **Competing Interests**

436 The authors declare that they have no competing interests.

437

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Author Contributions

Author V.H. designed the study, wrote the protocol, conducted the interviews, analyzed the data and written this manuscript. Author F.D.G., G.S. & A.C. were assigned as co-investigators in each hospital site and supervised patient recruitment and data gathering. Author A.T. & C.R. provided guidance and comments on the initial drafts of the study protocol including literature review, sampling, data gathering methods and ethical considerations. Author R.R. supervised the interviews, testing and scoring procedures for the school-based youth controls. Author M.T. worked with V.H. from the submission to approval of study protocol in the hospitals and over-all data gathering procedures. Author K.W. supervised the data gathering and provided guidance and comments on the analysis and the initial drafts of this manuscript. All authors have contributed to and have approved the final manuscript.

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Figure Legends

Fig. 1 Prevalence of paediatric and adult patients with borderline or clinical depression and anxiety. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. 2 Depression and anxiety mean scores among paediatric patients with DF and controls. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.