ACUTE KIDNEY INJURY IN DENGUE VIRUS INFECTION AMONG PEDIATRIC PATIENTS

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INTRODUCTION

Dengue is an acute febrile disease caused by an RNA virus that is transmitted by the bite of the *Aedes aegypti* mosquito. This pathology has been spreading to new locations, with an estimated incidence of over 100 million infections per year, of which 96 million present some degree of severity (1,2,3). This disease predominates in tropical and subtropical areas, which is why The Americas, Asia, and Africa are amongst the higher risk regions for the infection of dengue. According to the Pan American Health Organization, The Americas Region reported over 2.8 million cases of dengue in 2022, of which, over 22,000 were considered severe cases (4).

Between 2012 and 2018, the Dominican Republic, a country that shares the Caribbean island La Hispaniola with Haiti, experienced five disease out-breaks caused by mosquito-borne viruses where three of the five outbreaks were caused by dengue virus. In addition, the Pan-American Health Organization reports that serotypes 1, 2, and 4 were prevalent in the Caribbean between 2012 and 2014, and serotypes 2, 3, and 4 were circulating in the region in 2015 (14).

Depending on the clinical presentation of patients, dengue is classified according to the PAHO as dengue without warning signs (DNWS), dengue with warning signs (DWWS) and severe dengue (SD) (4). The latter, with high mortality and possible complications such as Acute Kidney Injury (AKI), which, in underdeveloped countries, can be the consequence of acute febrile illnesses, such as dengue (2,3,5).

The pediatric population between 0 and 15 years of age, are the most susceptible to sporadic cases of dengue, which represent an important cause of hospitalization and death in the pediatric population (5). With an incidence between 29.8 and 47.6 cases per every 1000 pediatric patients per year in India (6). AKI has shown to be a significant factor for mortality in dengue patients, but due to heterogeneity of data there is limited knowledge about AKI in dengue fever. Some studies have been conducted and determined an incidence ranging from 0.9% to 13.4% (2) and mortality increase ranging from 36% to 66% (6,7). Lastly, several studies demonstrated that patients with AKI had a longer length of hospital stay and higher morbidity, compared to those who did not present it (2,5,8).

In 2019, the Dominican Republic reported between seven to ten times higher cases of dengue than other countries in the Americas region (1). The Dominican Medical College, proposes that the basis of dengue outbreaks lies in the lack of water supply networks, where 36% of the population are forced to store water in tanks, therefore, creating mosquito breeding sites (9). These findings suggest that the pediatric population of the Dominican Republic is at increased risk of developing AKI, since there is no data available on the subject in the country, this study aims to evaluate the incidence of AKI in the pediatric population with dengue in the Dominican Republic.

METHODS

This was a hospital-based observational prospective study conducted at the Regional Children's Hospital Dr. Arturo Grullon, the main tertiary level pediatric healthcare center in the Northern Region of the Dominican Republic. The data collection process was carried out from December 2022 to April 2023 after permission was obtained from the Review Board, and ethical approval from a third party ethics committee. The diagnosis of dengue was done by signs and symptoms consistent with dengue, detailed in table 6 (10). Due to the descriptive and longitudinal nature of the project, a convenience sampling was proposed, enrolling all patients but those whose informed consent or informed assent were not obtained, patients with previous kidney injury and those with undetailed medical history, were excluded.

For evaluation of AKI, investigators took the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) score and the Renal Angina Index (RAI). In the case of pRIFLE, serum creatinine (Scr) and urine output are used in order to stratify the chance of AKI in the pediatric population (XA). To achieve this, researchers assumed that all patients presented adequate height for age and TGF was calculated based on the estimated surface area of patients. On the other hand, the RAI is based on changes in creatinine and severity of patients by using the need of ventilation, vasopressors , intense unit care (ICU) admission and the presence of a comorbidity (diabetes mellitus, chronic kidney disease or hypertension) as parameters (15).

Investigators also evaluated the role of dengue shock syndrome (DSS) in the development of AKI by comparing the results of pRIFLE and RAI, assuming that patients had normal albumin and that none of the participants had shock at the time of hospitalization.

STATISTICAL ANALYSIS

Data was evaluated with a statistical description using percentages and frequency, and for categorical variables absolute and relative frequency were used. On the other hand, due to obtaining less than one hundred cases, median and interquartile range were used for continuous variables.

The research team reserves the right to make use of subgroup analyses, multivariate analysis and inferential bivariate statistics in a *post-hoc* manner, making their use responsible and always specifying their nature after observing the data. None of these possible analyzes is based to confirm hypotheses, only to propose new hypotheses.

RESULTS

The sample was 44 as shown in **table 1**. The larger number of patients corresponded to the female gender representing 52.27%. Mild dengue frequency was present in 35 patients where 54.3% were female. Meanwhile, 9 patients had moderate dengue frequency in which 55.6% were male. Only 11.1% of participants with moderate dengue frequency notified previous history of dengue.

Variables	ALL	Mild Dengue Frequency (%)	Moderate Dengue Frequency (%)	P. overall	P. trend
		N=35	N=9		
Median , Q					
Sex				0.716	0.716
Female		54.3% [36.6%;71.2%]	44.4% 13.7%;78.8%		
Male		45.7% [28.8%;63.4%]	55.6% 21.2%;86.3%		
Age (months)		108 72.0;132	180 108;204	0.008	0.008
Previous History of Dengue				0.280	0.280
No		85.7% 69.7%;95.2%	77.8% 40.0%;97.2%		
Yes		0.00%0.00%;10.0%	11.1% 0.28%;48.2%		
Unspecified		14.3% 4.81%;30.3%	11.1% 0.28%;48.2%		
Sickle Cell Disease (Yes)		5.71% 0.70%;19.2%	0.00% 0.00%;33.6%	1.000	1.000
Time since probable infection (days)		4.00 4.00;6.00	5.00 4.00;6.00	0.496	0.496
Temperature (C)		37.1 37.0;37.2	37.0 36.5;38.3	0.976	0.976
Fever duration (Days)		4.00 4.00;5.00	4.00 4.00;17.0	0.243	0.243
Rash (Yes)		0.00% 0.00%;10.0%	11.1% 0.28%;48.2%	0.205	0.205
Petechiae (Yes)		0.00% 90.0%;100%	11.1% 0.28%;48.2%	0.205	0.205
Hematuria (erythrocyte/field)					
Negative		22.9% 10.4%;40.1%	44.4% 3.7%;78.8%		
Positive		8.57% [1.80%;23.1%]	11.1% 0.28%;48.2%		
Unspecified		68.6% 50.7%;83.1%	44.4% 13.7%;78.8%		
Hematocrit (%)		35.9 34.0;37.7	39.9 35.1;44.7	0.101	0.101
White Blood Cells (gb/microliter)		4.51 3.80;5.64	5.19 3.20;6.40	0.965	0.965
Platelets (cells/mm3)		44000 38000;62000	30000 23000;48000	0.023	0.023

Table 1: Demographic and infectious characteristics of pediatric patients with dengue from a tertiary healthcare center in Santiago, Dominican Republic.

In the case of hematuria, 8.57% of patients with mild dengue presented with hematuria while 11.1% of patients with moderate dengue showed positive results. 22.9% and 44.4% respectively, didn't present signs of hematuria. The remaining participants didn't specify the presence of this sign. **Table 1** also shows a relationship between lower platelet levels and the severity of dengue, with a p value of 0.023.

In regards to RAI and demographics and infectious characteristics of participants, **Table 3** shows a statistical relation with sickle cell disease and temperature for a p value of 0.020 and 0.039 respectively. When analyzing AKI, pRIFLE and RAI, a statistically significant relationship can be observed between AKI and GFR levels in the participants for a p value equal to 0.020 and 0.009, as shown in **Table 2** and **Table 3** respectively.

A significant association was registered when comparing GFR by body surface area with pRIFLE criteria (p=0.02), a decreased GFR was observed in patients who showed injury of 15.3 mg/mmol/1.73m2 (CI 95%, 12.3-17.2), while in patients with risk of injury the GFR reached up to 23.6 mg/mmol/1.73m2 (CI, 95% 21.6-24.4)

A significant association was found between Glomerular Filtration Rate (GFR) and Renal Angina Index(RAI), in which the reduction of the GFR was evident as RAI increased and vice-versa. Out of the studied patients, nine showed a RAI of 30 points, equating to a GFR of 17.9 mg/mmol/1.73m2 (CI 95%, 17.0-24.3) revealing an important renal failure

When comparing the use of pRIFLE and RAI when evaluating the risk of developing AKI among the participants, a significant relationship between the two can be perceived as shown in **Figure 1,** for a p value of 0.0037.

An additional analysis was carried out where only patients with injury and at risk of renal failure according to the pRIFLE classification were considered. Likewise, missing data were discarded and the difference between the groups was evaluated based on creatinine levels, age, and characteristics of the infection, such as alteration in white blood cell levels, platelet level, duration of infection and fever in days.

The possibility of having low creatinine levels in patients at risk of injury from the pRIFLE classification is lower compared to the group with injury, OR 0.33 (95% CI, 0.04-2.60). While it is more possible to present low levels of white blood cells in patients with injury, OR 1.03 (95% CI, 0.96-1.11). The group with injury was older than the group with risk of injury, OR 0.96 (95% CI, 0.69-1.34) as shown on **Table 4**. However, no association was found between changes in platelet number between groups. There was not enough evidence to reach statistically significant results.

In the group with moderate dengue, a higher creatinine level OR 2.97 (95% CI, 0.36-24.3) was observed, as well as a longer duration of fever OR 3.01 (95% CI, 0.27-34.0). However, the chance of having decreased white blood cells was lower in the moderate dengue group than in the mild dengue group OR 0.83 (95% CI, 0.21-3.21) (**Table 5**). The evidence was not sufficient to find statistically significant results.

Tabla 3: Renal failure clinical characteristics and its association with pRIFLE criteria groups of pediatric patients with dengue from a tertiary healthcare center in Santiago, Dominican Republic.

	Unchanged GFR	Risk	Injury	P overall
	N=3	N=4	N=4	
		Median , Q		
Creatinine (mg/dL)	0.79 0.75;0.87	0.60 0.55;0.76	1.31 0.43;2.41	0.756
GFR (mg/mmol/1.73m2)	24.7 24.5;27.4	23.6 21.6;24.4	15.3 12.3;17.2	0.020
GFR (mg/mmol)	67.9 64.4;73.2	77 67.5;81.3	52.8 26.7;79.9	0.741
Urea (mg/dL)	25.4 17.5;30.8	19.7 15.0;24.4	38.6 12.9;68.7	0.885
Diuresis (ml/kg/hr)	5.60 4.05;7.15	3.78 3.44;5.06	3.45 2.64;4.15	0.674

Table 4 Severity of dengue and infectious characteristics of pediatric patients with dengue from a tertiary healthcare center in Santiago, Dominican Republic.
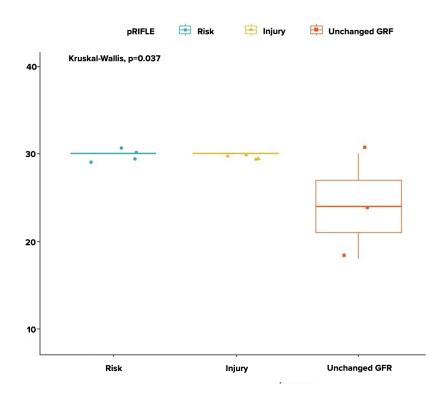
Variable	At risk	With injury	OR	P.overall
	N=4	N=4		
Creatinine (mg/dL)	1.31	0.60	0.33 [0.04;2.60]	0.885
White Blood Cells (gb/microliter)	5.00	26.7	1.03 [0.96;1.11]	0.083
Duration of fever (days)	4.00	4.00	2.25 [0.31;16.3]	0.508
Age (years)	7.50	6.00	0.96 [0.69;1.34]	1.000
Platelets (cells/mm3)	33000	39000	1.00 [1.00;1.00]	0.772

Table 5: Dengue Severity Category and infectious characteristics of pediatric patients with dengue from a tertiary healthcare center in Santiago, Dominican Republic.

Variable	Mild Dengue	Moderate Dengue	OR	P.overall
	N=7	N=1		
Creatinine (mg/dL)	0.58 [0.31;3.16]	2.16	2.97 [0.36;24.3	0.272
White Blood Cells (gb/microliter)	8.20 [3.80;45.3	5.19	0.83 [0.21;3.21]	0.513
Duration of fever (days)	4.00 [3.00;6.00]	5.00	3.01 [0.27;34.0]	0.211

Platelets (cells/mm3)	40000 [21000;179000]	24000	1.00 [1.00;1.00]	0.380

Figure 1: Description of the association between pRIFLE and Renal Angina Index of pediatric patients with dengue from a tertiary healthcare center in Santiago, Dominican Republic.

Despite being one of the countries with the most cases of dengue worldwide (1), in the Dominican Republic there are no current studies on the sociodemographic characteristics of pediatric patients with dengue and its possible complications, such as AKI. This study is the first step to continue exploring this line of research.

This study presents relevant data such as the statistical relationship between the severity of dengue and platelet levels, which is consistent with previous studies where a negative correlation is seen between both variables (11).

On the other hand, a large part of the participants, regardless of their dengue severity, did not present hematuria during their admission to the hospital. This contrasts with previous studies where patients with severe dengue manifested bleeding with a statistically significant value (5). This could have been related to the small number of patients and the specification of the presence or absence of this sign during the taking of the clinical history.

One of the most critical and explicit data points in this report would be the difference between the use of pRIFLE and RAI when evaluating AKI in these patients, which is reflected in Figure 1 and represents a more pragmatic use of pRIFLE versus RAI. . This is supported by previous studies showing that the prevalence of AKI increased when changes in estimated GFR (eGFR) (pRIFLE) were taken into account instead of changes in Cr in hospitalized pediatric patients (12,13). We understand that the statistical significance of these results would be confirmed by increasing the power of a future study.

Several factors must be considered when evaluating the results. A crucial aspect is the fact that for each patient it had to be assumed that the patients had adequate height for age to establish GFR and to be able to use pRIFLE effectively. Likewise, GFR had to be calculated based on the surface area of each participant. This is due to the lack of resources in the medical center where the investigation in question was carried out. Likewise, it should be taken into account that each diagnosis of dengue among the participants was made based on the symptoms and CBC of the participants. Although it is a support method to reach the diagnosis (9), there are more precise and objective tests. such as virus isolation (VI), reverse transcription-polymerase chain reaction (RT-PCR), haemagglutination inhibition (HI), and enzyme-linked immunosorbent assay (ELISA) for the detection of dengue non-structural antigen-1 (NS1) or dengue -specific immunoglobulin (IgM/IgG) to confirm diagnosis (10). The researchers propose to implement some of these tests in the future for a better diagnostic method and clinical management of patients in public pediatric centers.

We recognize the lack of homogeneity in reporting signs and symptoms and the small number of participants. Also, we see the heterogeneity of variable distribution as a weakness such as hematuria, previous history of dengue, diuresis, urea and creatinine. All of this represents an opportunity to reconsider new lines of research related to AKI in pediatric patients with dengue in the future with a deeper focus on this center and possibly linking other centers in the country.

CONCLUSION

These results are an excellent framework to work upon and create a proper national characterization of pediatric patients with dengue by expanding the number of participants and by including other pediatric centers in the country in order to better characterize the sociodemographics of the disease in this population.

The limited access to diagnostic methods and lack of use of precise and objective diagnostic tools can explain the country's low number of studies related to dengue and the possible complications of this disease, including AKI. Which prompts evaluation and exploring the possible solutions for better management of patients.

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Table 6: Dengue fever diagnostic criteria

Dengue without warning signs	Dengue with warning signs	Severe dengue
Traveling within the last 14 days to areas with high dengue transmission	After fever cessation presenting with one of the following	Every case of dengue with one of the following finding
Nausea or vomiting	Intense abdominal pain	Shock
Headaches or arthralgias	Persistent vomiting, mucosal bleeding	Respiratory distress
Petechiae or positive tourniquet test	Ascites, pleural effusion, pericardial effusion	Severe bleeding
Leukopenia	Lethargy, irritability, hepatomegaly	Multi-organ damage
Children with 2 - 7 days of fever without an apparent focus.	Thrombocytopenia, progressive hematocrit increase	