

ORIGINAL ARTICLE

MEAN HEMATOCRIT VALUES, DISEASE SEVERITY, AND DISCHARGE STATUS OF UNDERNOURISHED VERSUS WELL-NOURISHED CHILDREN WITH DENGUE INFECTION IN A TERTIARY GOVERNMENT HOSPITAL

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ABSTRACT

Background: Studies comparing hematocrit values, disease severity, and discharge status between well-nourished and undernourished pediatric dengue patients are limited.

Objective: This study compared the mean hematocrit values, disease severity and discharge status of undernourished vs. well-nourished pediatric dengue patients admitted in a tertiary government hospital.

Methodology: A retrospective cohort study involving 114 pediatric dengue patients, with comparison groups of well-nourished and undernourished children matched according to age, phase of illness and sex was done. Main outcomes measured were mean hematocrit values, disease severity and discharge status.

Results: There was a significantly lower mean pre-resuscitation hematocrit in the wasted ($M=39.67\%$, $SD=3.78$) compared to the well-nourished group ($M=43.68\%$, $SD=4.72$), $p=0.006$, among children >6 to 12 years old in the febrile phase. There were no significant differences in disease severity and discharge status between wasted and well-nourished children. In those >2 to 6 years old in the febrile phase, the severely wasted had significantly higher pre-resuscitation hematocrit ($M=43.28\%$, $SD=4.77$) compared to well-nourished children ($M=39.11\%$, $SD=5.34$), $p=0.041$. More severe dengue, worse discharge status and an earlier time to demise was seen among severely wasted children.

Conclusion: Wasted participants had significantly lower mean hematocrit values with no difference in disease severity and discharge status when compared to well-nourished participants. Severely wasted children had significantly higher hematocrit values, severe dengue, and worse discharge status.

KEYWORDS: *Dengue Fever, Undernutrition, Hematocrit*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

INTRODUCTION

The World Health Organization reported in 2018 that 50 to 100 million dengue cases occur annually worldwide.¹ In the Philippines, as of 2019, dengue is the 2nd leading cause of death and 6th most common cause of mortality among communicable diseases in the 5 to 14 year age group.² In August of the same year, the Department of Health declared a national dengue epidemic in the country; and in the institution where this study was conducted, there was a noted increase of pediatric dengue cases in 2019 from 1,549 to 1,803, with a case fatality rate of 2.9%.³⁻⁴

Since dengue is a vector-borne systemic viral disease with a wide clinical spectrum ranging from mild flu-like symptoms to more severe manifestations (including persistent vomiting, severe abdominal pain and hypotension), early detection is crucial to management.⁵⁻⁶ Laboratory tests to establish the diagnosis include detection of viral nucleic acid, antigens and antibodies. In areas with limited resources, clinicians rely on clinical manifestations and hematologic findings of decreasing platelet with concomitant rise in hematocrit.⁶

A local study done by Lim, Gatchalian and Capeding on two-hundred dengue patients aged 0 to 19 years old and admitted at the Research Institute for Tropical Medicine from 2000-2004 showed hematocrit values to have ranged from 29 to 64% (M=42%, SD=5).⁷ The subjects included were admitted between one to ten days from start of clinical symptoms, however, nutritional status as well as timing of hematocrit determination were not identified. An elevated hematocrit for age or a rise of at least 20% from baseline warrants immediate attention, thus hematocrit monitoring plays an essential role in dengue management.⁶

Undernutrition is known to decrease hematocrit levels.

A study done by Gebreegziabier, *et al.* revealed that anemia is generally more common in children who are wasted and severely wasted, and hemoglobin levels of undernourished children were relatively lower compared to those who are well-nourished.⁸ Another study by Arya, *et al.* showed that about 95% of children aged 6 months to 5 years old with severe acute malnutrition had anemia with a mean hemoglobin level of 7.17 ± 2.26 gm/dL and a mean hematocrit level of $21.27 \pm 6.63\%$.⁹ Their healthy counterparts, on the other hand, had a mean hemoglobin level of 9.22 ± 3.362 gm/dL and a mean hematocrit level of $27.40 \pm 8.98\%$. Although hematocrit levels were compared between undernourished and well-nourished participants, patients in both studies did not have dengue infection.

Mogra, *et al.* looked into the hematologic profile of 100 dengue patients - 8% of whom are severely wasted and 28% moderately wasted. All patients with severe dengue had hemoconcentration compared to only 70% in those with dengue with warning signs. This supports reviews that hemoconcentration is a prognostic factor for disease severity. The study, however, did not look into the effect of nutritional status on hematocrit levels and disease severity.¹⁰ In another study of 4,532 dengue cases in Thailand from 1995 to 1999, a look into the nutritional status of participants revealed that 65 to 67% were well-nourished, 9 to 11% had moderate to severe malnutrition and 23 to 24% were overweight or obese.¹¹ The clinical signs, symptoms and laboratory findings were almost the same between the malnourished and those with normal nutritional status. However, about 37.8% of wasted and severely wasted patients developed shock compared to those with normal nutritional status where only 29.9% presented with shock. Moreover, a greater number of mortalities were identified in the malnourished group compared to those with normal nutritional status with a case fatality rate of 0.5% and 0.07%, respectively.

This contrasts with the 2020 study of Maneerattanasak and Suwanbamrung where undernutrition did not pose a greater risk of having severe type of dengue, although it appeared as a protective factor against dengue hemorrhagic fever and dengue shock syndrome. Only overweight and obese patients were found to have a higher risk in developing severe type of dengue infection.¹²

To date, there have been several studies done on undernutrition and dengue infection, but the effects of the former on mean hematocrit values, dengue disease severity and discharge status have not been explored. Hence, this study determined and compared pre-resuscitation hematocrit values, disease severity and discharge status between undernourished versus well-nourished pediatric dengue in-patients.

MATERIALS AND METHODS

Study Design

This is a retrospective cohort study approved by the Ethics Review Committee of the Education, Training, and Research Board. Outcomes assessed were hematocrit values, disease severity (dengue with warning signs or dengue severe) and discharge status (improved or expired) of the exposed group (those with undernutrition) and the unexposed group (those who are well-nourished).

Study Population and Setting

Included were patients aged 0-17 years old admitted for the first time in a tertiary government referral and training hospital from January 1 to December 31, 2019 with a final diagnosis of dengue with warning signs or dengue severe, with documented hematocrit levels prior to any fluid resuscitation.

Excluded were overweight and obese patients as they have significantly higher hematocrit values and a more severe type of dengue;¹³ patients referred from other institutions who received intravenous fluid resuscitation before baseline hematocrit determination; and patients with other known co-morbidities such as hematologic, renal, cardiac disease or concomitant bacterial infections as these conditions naturally alter the hemogram. Subjects who presented with severe bleeding and those needing blood transfusion at the time of hematocrit determination were also excluded.

Methodology

Review of medical records was done and patients with a final diagnosis of dengue with warning signs or dengue severe from January to December 2019 were identified using the master list provided by the Medical Records Section. Cases were grouped according to nutritional status using the height and weight on admission and assessed based on the World Health Organization growth charts 2007.¹⁴ Wasted and severely wasted patients were identified and sampled consecutively. Data on hematocrit value, age, sex, phase of illness, disease severity and discharge status were collected. For expired patients, time to demise was determined and categorized as expired less than or more than 48 hours from admission. Well-nourished dengue patients were also identified, sampled consecutively and matched with the undernourished group based on age, sex and phase of illness to control for confounding variables. Patients were grouped into the following age categories: >2 to 6 years old, >6 to 12 years old, and >12 to 17 years old. These age clusters were used as there are set hematocrit values per age category. Patients were also matched according to sex for the >12 to 17-year-old age group since there is a difference in the normal hematocrit values between sexes.¹⁵

Lastly, patients were matched according to phase of illness since a rise in hematocrit is more evident during the critical phase due to plasma leakage.

Sample Size

Based on the study of Kalayanarooj and Nimmannitya, the sample size was calculated using the difference of two proportions formula, with a hypothetical proportion of 10% undernourished patients with dengue infection and 66% well-nourished patients with dengue infection, with 95% confidence interval.¹¹ A sample size of at least 15 participants per subgroup was calculated. We included 114 patient records, with 57 well-nourished and 57 undernourished (36 wasted and 21 severely wasted) patients, which is more than the sample size calculated.¹⁶

Statistical Analysis

Data were analyzed using the software SPSS. Descriptive studies were used to analyze demographic data. Independent samples T-test was used to compare the mean hematocrit values of well-nourished and undernourished patients. Chi-square was used to compare differences in disease severity and discharge status between groups and time to demise was analyzed using Fisher’s Exact Test.

RESULTS

A total of 1,803 pediatric dengue cases were recorded in the hospital for 2019, however only 114 subjects were included and reviewed by consecutive sampling due to the rigorous matching process. As seen in Table 1, half (N=57, 50%) were identified as well-nourished and the rest (N=57, 50%) were classified as undernourished. The latter group was further classified into wasted (36) and severely wasted (21).

Matched well-nourished and wasted patients were mostly males (N=43, 59.7%), >6 to 12-year-olds (N=46, 63.9%), residing within Cagayan de Oro City (N=46, 63.9%), referred from other institutions (N=40, 55.6%) and were in the febrile phase of illness (N=54, 75%) at the time hematocrit values were obtained. As for matched well-nourished and severely wasted patients, an equal number of males and females were observed, majority were in the >2 to 6 years old age group (N=20, 47.6%) and residing outside the city (N=22, 52.4%). When comparing matched well-nourished and severely wasted subjects, 17 of 21 well-nourished patients were walk-ins (N=17, 81%). In contrast, those who were severely wasted were referrals from other institutions (N=14, 66.7%). Majority of subjects were in the febrile phase (N=40, 95.2%) when hematocrit values were obtained.

Table 1. Nutritional Status and Sociodemographic Profile of Patients with Dengue Infection

Parameter	Well-nourished	Wasted	Total		Well-nourished	Severely Wasted	Total	
	N	N	N	Percentage (%)	N	N	N	Percentage (%)
Gender								
Male	22	21	43	59.7%	12	9	21	50%
Female	14	15	29	40.3%	9	12	21	50%
Age group								
>2 to 6 years old	9	9	18	25%	10	10	20	47.6%
>6 to 12 years old	23	23	46	63.9%	9	9	18	42.9%
>12 to 17 years old	4	4	8	11.1%	2	2	4	9.5%
Address								
Within CDO	25	21	46	63.9%	10	10	20	47.6%
Outside CDO	11	15	26	36.1%	11	11	22	52.4%
Source								
Walk-in	15	17	32	44.4%	17	7	24	57.1%
Referral	21	19	40	55.6%	4	14	18	42.9%
Phase of Illness								
Febrile phase	27	27	54	75%	20	20	40	95.2%
Critical phase	9	9	18	25%	1	1	2	4.8%

Table 2 shows that there is a statistically significant difference in mean hematocrit values between well-nourished and wasted patients among those >6 to 12 years of age in the febrile phase, with wasted patients having a lower mean hematocrit (M=39.67%, SD=3.78) compared to well-nourished patients (M=43.68%, SD=4.72), p=0.006. When comparing well-nourished and severely wasted patients in the febrile phase, there is a statistically significant difference in mean hematocrit among patients >2 to 6 years of age, with the severely wasted having higher hematocrit levels (M=43.28%, SD=4.77) compared to well-nourished patients (M=39.11%, SD=5.34), p=0.041. Comparison between mean pre-resuscitation hematocrit values of well-nourished versus wasted patients, as well as well-nourished versus severely wasted patients, is seen in Table 2.

Table 2. Mean Hematocrit Values between Well-nourished vs. Wasted and Severely Wasted Pediatric Dengue Patients

Phase of illness	Age group	Mean and Standard Deviation of Hematocrit Values (%)		P-value	Mean and Standard Deviation of Hematocrit Values (%)		P-value
		Well-nourished	Wasted		Well-nourished	Severely Wasted	
Febrile phase	>2 to 6 years old	37.8 ± 4.30	37.64 ± 3.00	0.466	39.11 ± 5.34	43.28 ± 4.77	0.041
	>6 to 12 years old	43.68 ± 4.72	39.67 ± 3.78	0.006	38.99 ± 2.08	39.90 ± 3.35	0.262
	>12 to 17 years old						0.410
	Male	46.9 ± 7.14	44.87 ± 7.01	0.301	40.10 ± 1.27	40.35 ± 0.49	
	Female	44	41.9	n/a	-	-	
Critical Phase	>2 to 6 years old	34	34.5	n/a	-	-	-
	>6 to 12 years old	38 ± 8.62	36.7 ± 3.67	0.431	41	53.2	n/a
	>12 to 17 years old						
	Male	40.3	43.5	n/a	-	-	-

Table 3 shows that 17 of 36 wasted patients were diagnosed with dengue with warning signs and 19 were diagnosed with dengue severe. On the other hand, half (50%) of well-nourished patients had dengue with warning signs and the other half had dengue severe.

Of the twenty-one severely wasted patients with dengue infection, six had dengue with warning signs and majority (N=15) had dengue severe. In contrast, majority (N=16) of the well-nourished were diagnosed with dengue with warning signs and only five were diagnosed with dengue severe. As to association between nutritional status and disease severity, there was no significant difference between the wasted and their matched well-nourished counterparts with a p-value of 0.814, but a significant difference was seen between the severely wasted and their well-nourished counterparts, p=0.02.

Table 3. Association between Nutritional Status and Disease Severity among Pediatric Dengue Patients

Disease Severity	Nutritional Status (N)		P-value	Nutritional Status(N)		P-value
	Well-nourished	Wasted		Well-nourished	Severely Wasted	
Dengue with Warning signs	18	17	0.814	16	6	0.02
Dengue Severe	18	19		5	15	
Total	36	36		21	21	

Table 4 shows that there is no significant difference in discharge status between wasted patients and their matched well-nourished counterparts, p=0.326. However, there is a significant difference in discharge status when comparing severely wasted patients with those with normal nutritional status, with eleven (52.4%) severely wasted being discharged improved while ten expired (47.6%), in contrast to matched well-nourished patients who were all discharged improved, p <0.001. Among those who expired, there is no significant difference in time to demise from admission when comparing the wasted group compared to their well-nourished counterparts, p=0.348. However, there was a significant difference between severely wasted patients compared to their well-nourished counterparts, with eight severely wasted patients expiring with only less than 48 hours of hospital stay, p <0.001.

All ten severely wasted patients who expired were referrals from other institutions and were managed for more than 4 hours before transfer. Time to demise in this study only included the number of hours the subjects stayed in the hospital where the study was conducted.

Table 4. Association between Nutritional Status and Discharge Status among Pediatric Dengue Patients

Parameter		Nutritional Status (N)		P-value	Nutritional Status (N)		P-value
		Well-nourished	Wasted		Well-nourished	Severely Wasted	
Discharge Status	Improved	32	29	0.326	21	11	<0.001
	Expired	4	7		0	10	
Time to Demise of Expired Patients	<48 hours	1	4	0.348	0	8	<0.001
	>48 hours	3	3		0	2	

DISCUSSION

When comparing the wasted population and their well-nourished counterparts, no significant differences in disease severity and discharge status were seen in this study. This is consistent with the study of Maneerattanasak and Suwanbamrung which showed that children who developed dengue hemorrhagic fever were less likely undernourished than were healthy controls. This finding support theories that undernutrition is associated with a dysfunction of the innate and adaptive immune system, thus hindering an exaggerated host immune response, which plays a pivotal role in the pathogenesis of severe dengue.¹² This is contrary to the study of Kalayanaroj and Nimmannitya in Thailand, which showed that when malnourished patients contracted dengue fever, they presented with severe disease, had a higher risk of developing shock and had higher case fatality rates.¹¹ However, this study did not sub-categorize malnutrition into wasting and severe wasting.¹¹

Gebregziabiher, *et al.* noted that baseline hemoglobin and hematocrit levels of undernourished children were significantly lower compared to their well-nourished counterparts.⁸ However, it does not follow that they will have a lower percentage rise in hematocrit when they develop dengue fever. In our study, it was shown that >2 to 6 years old severely wasted children with dengue had significantly higher mean hematocrit values compared to their well-nourished counterparts. Hemoconcentration among the severely wasted may be a sign of rapid deterioration. This study also showed that more severe disease and worse clinical outcomes are significantly associated with the severely wasted, but not the wasted population. More severely wasted patients developed shock, deteriorated and eventually expired. These findings were consistent with those of Kalayanaroj and Nimmannitya, where malnourished patients had a greater risk of developing dengue shock syndrome with a higher case fatality rate. These were attributed to the smaller extra-cellular and plasma volumes of undernourished children, thus shock develops more rapidly even with a lesser degree of plasma leakage.¹¹ Given this hypothesis, physicians should closely monitor severely wasted children for early signs of severe disease.

There were several limitations encountered in our study as follows: It was retrospective in nature and was done in a single-center, thus findings cannot be generalizable to the population at large. The gold standard for the diagnosis of dengue fever was not available for use in our study, and since there were participants who were referrals from other institutions with documented pre-resuscitation hematocrit values, not one machine was used in hematocrit determination. This in turn could have been affected by machine calibration. Association of hematocrit values with disease severity and discharge status was also not done.

In an attempt to control for confounding variables, there were age groups with only one subject per subgroup, thus significant differences in hematocrit values cannot be established. Lastly, a substantial number of participants were not included due to limitations in the matching process.

Further studies are recommended with the inclusion of a control group with more participants to be able to establish hematocrit values among Filipino children with dengue with varying nutritional status.

CONCLUSION

Wasted participants had significantly lower mean hematocrit values with no difference in disease severity and discharge status when compared to well-nourished participants. Severely wasted children had significantly higher hematocrit values with severe dengue and worse discharge status.

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