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Clinicopathological Profile of Dengue Infection in a Tertiary Care Centre in Nepal

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ABSTRACT

Background: Dengue is a mosquito-borne viral disease with a wide spectrum of presentations ranging from subclinical disease to severe dengue. Dengue is endemic to the Terai of Nepal. Interestingly, an increasing incidence has been reported from hilly areas like Kathmandu valley.This study explored the clinicopathological profile of dengue infection.

Methods:A total of 84 serologically confirmed dengue cases from September to November 2019 at KIST Medical College were recruited in a cross-sectional study after obtaining ethical approval. Dengue was categorized as dengue without warning signs, dengue with warning signs, and severe dengue. Clinicopathological information was recorded in the proforma by reviewing patients' records. A descriptive statistical tool and chi-square test were carried out.

Results: Out of 84 patients, 76% (64) were dengue without warning signs, 21.4% (18) were dengue with warning signs and 2.4% (2) were severe dengue. About 97.6% (82) presented with fever. During the course of illness, anemia was identified in 38.1% (32), thrombocytopenia in 65.5% (55), hemoconcentration in 6% (5), and leucopenia in 82.1% (69). Similarly, elevated aspartate transaminase and alanine transaminase (ALT) was observed in 67.7% (42) and 53.2% (33) respectively. The severity of dengue on presentation to hospital was significantly associated with thrombocytopenia, leucopenia, and elevated ALT. Similarly, the severity during course of illness in hospital was significantly associated with hemoconcentration, thrombocytopenia, leucopenia, and elevated ALT.

Conclusions: Most common presentation of dengue infection was fever.The most common laboratory abnormalities were leucopenia, thrombocytopenia, hemoconcentration, anemia, and elevated liver enzymes. Awareness of these clinical and laboratory parameters is important for the prompt diagnosis, severity estimation, and overall management of dengue infection.

Keywords: Biochemical; dengue; hematological; Nepal; serological

INTRODUCTION

Dengue is a mosquito-borne viral disease. The disease spectrum ranges from subclinical to severe dengue and primarily presents with a high fever.[1,2] World health organization (WHO) classified dengue as dengue (with or without warning signs) and severe dengue.[1]

Dengue has spread widely in all WHO regions with frequent outbreaks and increasing mortality in past decades.[1] Several dengue outbreaks had occurred in Nepal since its first case was isolated in 2004 .[3,4] Dengue was endemic and primarily found in the Terai region until 2010, but was increasingly detected in the hilly region in 2016. [5] An increase in average temperature, unplanned urbanization, poor sanitation are a few factors responsible for dengue spread in higher altitude regions like Kathmandu Valley. [2, 6] The dengue outbreak 2019 is a recent event of significant magnitude in the Kathmandu Valley. This study explored the clinicopathological profile of dengue infection during the dengue outbreak in 2019.

METHODS

The cross-sectional study was conducted at KIST Hospital during a duration of three months. Ethical clearance was

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obtained from the institutional review committee (IRC No. 077/078/13). All the hospitalized cases of dengue infection confirmed by serological tests from September to November 2019 were enrolled in the study.

Patients who had fever with positive serology for dengue (rapid diagnostic test by Biotrol lot no: 16A0919) were included in the study while patients without fever and co-existence of other infectious diseases were excluded. Positive test results for NS1 antigen or Dengue IgM or both were considered positive dengue serology. Eighty-eight patients with a serological diagnosis of dengue were studied which represented 100% of cases during the study period. Four of them were excluded due to repeated admission and co-existence of scrubs typhus, Japanese encephalitis and urinary tract infections. Thus 84 patients were enrolled in the study. Data were obtained retrospectively by reviewing patients' records from the medical records and organized in a proforma. The patient's history and physical examination along with hematological, biochemical, microbiological, and serological findings documented during admission and the course of hospitalization were evaluated and analyzed.

Based on the clinicopathological parameters, patients were categorized into three different clinical types according to the WHO classification 2009, dengue without warning signs, dengue with warning signs, and severe dengue.[1] Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement >2 cm, and increase in hematocrit concurrent with a rapid decrease in platelet count. While in severe dengue there is severe plasma leakage leading to shock and fluid accumulation with respiratory distress, severe bleeding, and severe organ involvement (liver: aspartate transaminase (AST) or alanine transaminase (ALT) ≥1000, impaired consciousness and heart, and other organs).[1,2]

Thrombocytopenia is defined as a platelet count of fewer than 150,000 cells /mm^3. Anemia is defined as a hemoglobin level of less than 13 gm/dl (male) and less than 12 gm/dl (female). Hemoconcentration is defined as pack-cell volume (PCV) of more than 52% (male) and more than 47% (female). Leucopenia is defined as a total white blood cell count of fewer than 4,500 cells/mm^3. Elevated AST and ALT are considered when the level is more than 40 IU/L and 56 IU/L respectively. [2,4,7]

Following the classification, the clinical, biochemical, and haematological profiles were compared and analyzed. Data entry and analysis were done using SPSS 26 version. Descriptive statistics and chi-square test were carried out to generate results to meet our objectives. A p-value of 0.05 was taken as significant.

RESULTS

Among 84 patients, 67.9% (57) were diagnosed as dengue without warning signs (Den. without WS), 29.8% (25) as dengue with warning signs (Den. with WS), and 2.4% (2) were diagnosed as severe dengue (Severe Dengue).

The patients ranged from three to 82 years of age with a mean age of 35.3 ± 16.6 years. The association between age group and severity of disease (dengue) was significant (p-value 0.035) (Table 1). Males constituted 53.6% (45) of patients (Table 1).

Around 90.48% (76) were NS1 antigen and 3.57% (3) was IgM only positive. The association between NS1 antigen positivity and severity of disease (dengue) was significant (p-value 0.001) (Table 1).

Most cases were admitted during September, 60.7% (51) followed by 35.7% (30) in October while 3.6% (3) were admitted as late as November. The majority 94.05% (79) had a fever as the first symptom. At presentation to hospital, 97.6% (82) patients presented with fever. However, remaining two patients who didn't have fever on presentation developed fever on the first day of admission. Headaches, body ache, retrobulbar pain, rashes, abdominal pain, vomiting and cough were observed in 77.4% (65), 73.8% (62), 48.8% (41), 21.2% (18), 19% (16), 14.3% (12) and 6% patients respectively. The bleeding manifestation was present in 7.1% (6) (epistaxis, gum bleeding, and per rectal bleeding). The presence of bleeding manifestations (p-value 0.017) and retrobulbar pain (p-value 0.007) was significantly associated with the severity of dengue (Table 1).

Twenty-two patients had co-morbidities of which 11.9% (10) were hypertensive, 4.8% (4) had diabetes and hypothyroidism each. The presence of co-morbidities and severity of disease had a significant association (p-value 0.036) (Table 1).

Table 1. Demographic, clinical, and serological features of dengue patients.

		Dengue without WS	Dengue with WS	Severe Dengue	Total	P-value
Age distribution (N=84)						
<15 year		7.1% (6)	0	0	7.1% (6)	0.035
15-64		58.3% (49)	25% (21)	1.2% (1)	84.5% (71)	
>=65		2.4% (2)	4.8% (4)	1.2% (1)	8.3% (7)	
Total		67.9% (57)	29.8% (25)	2.4% (2)	100% (84)	
Gender distribution (N=84)						
Male		36.9% (31)	15.5% (13)	1.2% (1)	53.6% (45)	0.975
Female		31% (26)	14.3% (12)	1.2% (1)	46.4% (39)	
Symptoms						
Fever	Yes	67.9% (57)	27.4% (23)	2.4% (2)	97.6% (82)	0.084
	No	0	2.4% (2)	0	2.4% (2)	
Headache	Yes	56% (47)	20.2% (17)	1.2% (1)	77.4% (65)	0.252
	No	11.9%(10)	9.5% (8)	1.2% (1)	22.6% (19)	
Body ache	Yes	51.2% (43)	21.4% (18)	1.2% (1)	73.8% (62)	0.728
	No	16.7% (14)	8.3% (7)	1.2% (1)	26.2% (22)	
Retrobulbar pain	Yes	40.5% (34)	8.3% (7)	0	48.8% (41)	0.007
	No	27.4% (23)	33.3% (28)	2.4% (2)	51.2% (43)	
Rashes	Yes	17.9% (15)	3.6% (3)	0	21.4% (18)	0.198
	No	50% (42)	26.2% (22)	2.4% (2)	78.6% (66)	
Pain Abdomen	Yes	11.9% (10)	6% (5)	1.2% (1)	19% (16)	0.587
	No	56% (47)	23.8% (20)	1.2% (1)	81% (68)	
Bleeding	Yes	1.2% (1)	6% (5)	0	7.1% (6)	0.017
	No	66.7% (56)	23.8% (20)	2.4% (2)	92.9% (78)	
Co-morbidities	Yes	13.1% (11)	8.3% (7)	2.4% (2)	23.8% (20)	0.036
	No	54.8% (46)	21.4% (18)	0	76.2% (64)	
Serology						
NS1 Antigen	Yes	60.7% (51)	29.8% (25)	0	90.5% (76)	0.001
	No	7.1% (6)	0	2.4% (2)	9.5% (8)	
IgM Antibody	Yes	3.6% (3)	0	0	3.6% (3)	0.304
	No	64.3% (54)	29.5% (25)	2.4% (2)	96.4% (81)	

On presentation, hemoglobin ranged from 9.6 to 18.5 gm/dl. Platelet counts (n=78) ranged (34,000 to above 4, 50,000) cells/mm^3 while maximum hematocrit was 49.5% for male and 49.2% for female. Total leucocyte count (n=77) ranged from 1800 to 16800/mm^3. Maximum AST (n=42) and ALT (n=43) was 386 IU/L and 232 IU/L respectively.

During the course of illness in the hospital, the maximum hematocrit recorded was 51%, hemoglobin ranged from 9.6 to18.8 gm/dl, platelet counts ranged from (14,000 to 471,000)/mm^3 and leucocyte counts ranged from 1,800 to 16,800/mm^3. Maximum AST and ALT were recorded at 1,100 IU/L and 349 IU/L respectively.

The levels of thrombocytopenia on the day of presentation (p-value 0.03) and during the course of illness in the hospital (p-value <0.001) was significantly associated with the severity of dengue (Table 2).

Table 2. Association of the level of thrombocytopenia with the severity of dengue.

DIAGNOSIS	(<=50000) /mm3	(>50000-100000)	(>100000-150000)	(>150000)	P-value
Thrombocytopenia at Presentation (N=78)					
Den. without WS	0	2.6% (2)	14.1% (11)	55.1% (43)	0.03
Den. with WS	1.3% (1)	3.8% (3)	10.3% (8)	10.3% (8)	
Severe Dengue	0	1.3% (1)	0	1.3% (1)	
Total	1.3% (1)	7.7% (6)	24.4% (19)	66.7% (52)	
Thrombocytopenia during the course of illness in hospital (N=84)					
Den. without WS	0	6% (5)	31% (26)	31% (26)	0.000
Den. with WS	6% (5)	10.7% (9)	10.7% (9)	2.4%(2)	
Severe Dengue	0	1.2% (1)	0	1.2% (1)	
Total	6% (5)	17.9% (15)	41.7% (35)	34.5% (29)	

Table 3. Association of hematological and biochemical parameters with the severity of dengue on presentation to hospital.

At presentation to hospital	Severity of Dengue	Percentage (frequency)		P- value
		Yes	No	
Anemia (n=81)	Den. without WS	14.8% (12)	55.6% (45)	0.600
	Den. with WS	7.4% (6)	19.8% (16)	
	Severe Dengue	1.2% (1)	1.2% (1)	
	Total	23.5% (19)	76.5% (62)	
Hemoconcentration (n=79)	Den. without WS	0	70.9% (56)	0.066
	Den. with WS	2.5% (2)	24.1% (19)	
	Severe Dengue	0	2.5% (2)	
	Total	2.5% (2)	97.5% (77)	
Thrombocytopenia (n=78)	Den. without WS	16.7% (13)	55.1% (43)	0.012
	Den. with WS	15.4% (12)	10.3% (8)	
	Severe Dengue	1.3% (1)	1.3% (1)	
	Total	33.3% (26)	66.7% (52)	
Leucopenia (n=77)	Den. without WS	46.8% (36)	24.7% (19)	0.021
	Den. with WS	22.1% (17)	3.9% (3)	
	Severe Dengue	0	2.6% (2)	
	Total	68.8% (53)	31.2% (24)	
Elevated AST (n=42)	Den. without WS	35.7% (15)	31% (13)	0.742
	Den. with WS	21.4% (9)	11.9% (5)	
	Total	57.1% (24)	42.8% (18)	
Elevated ALT (n=43)	Den. without WS	23.3% (10)	44.2% (19)	0.021
	Den. with WS	23.3% (10)	9.3% (4)	
	Total	46.5% (20)	53.5% (23)	

On presentation, anemia, leucopenia, and thrombocytopenia were observed in 23.5%, 68.8%, and 33.3% of patients. The presence of thrombocytopenia, leucopenia, and elevated ALT on presentation was significantly associated with the severity of dengue with a p-value of 0.012, 0.021, and 0.021 respectively (Table 3).

Total days of illness at the time of presentation to hospital ranged from (1 to 10) days with a mean of 3.6± 2.6 days.

During the course of illness in the hospital, anemia, leucopenia, and thrombocytopenia were present among 38.1%, 82.9%, and 65.5% of patients respectively. Hemoconcentration was present in only 6% of patients. Elevated AST, ALT, and ALP were found in 67.7%, 53.2%, and 5.3% patients respectively (Table 4). The presence of hemoconcentration, thrombocytopenia, leucopenia, elevated ALT, and ALP during the course of illness in the hospital was significantly associated with the severity of dengue with a p-value of 0.002, 0.002, 0.011, 0.023, and 0.02 respectively (Table 4).

The total duration of admission ranged from (1 to 12 days) with a mean of 4.5± 2.1 days.

Day of illness (DOI) means duration from the appearance of first symptoms. Prevalence of thrombocytopenia increased as DOI and DOA progressed. It ranged from 30.7% (4) on first to 60.7% (17) on fifth DOI and 33.3% (26) first day to 78.6% (11) on fifth DOA. The prevalence of leucopenia was high and gradually increased. It was in 88.6% (39) on the fourth DOI and 61% (46) on the second DOA (Figure 1).

Table 4. Association of hematological and biochemical parameters with the severity of dengue during the course of illness in hospital.

During course illness in hospital	Severity of the disease	Percentage (frequency)		P-value
		Yes	No	
Anemia (n=84)	Den. without WS	22.6% (19)	45.2% (38)	0.092
	Den. with WS	13.1% (11)	16.7% (14)	
	Severe Dengue	2.4% (2)	0	
	Total	38.1% (32)	61.9% (52)	
Hemoconcentration (n=84)	Den. without WS	0	67.9 (57)	0.002
	Den. with WS	6% (5)	23.8% (20)	
	Severe Dengue	0	2.4% (2)	
	Total	6% (5)	94% (79)	
Thrombocytopenia (n=84)	Den. without WS	36.9% (31)	31% (26)	0.002
	Den. with WS	27.4% (23)	2.4% (2)	
	Severe Dengue	1.2% (1)	1.2% (1)	
	Total	65.5% (55)	34.5% (29)	
Leucopenia (n=84)	Den. without WS	54.8% (46)	13.1% (11)	0.011
	Den. with WS	27.4% (23)	2.4% (2)	
	Severe Dengue	0	2.4% (2)	
	Total	82.1% (69)	17.9% (15)	
Increased AST (n=62)	Den. without WS	40.3% (25)	24.2% (15)	0.369
	Den. with WS	25.8% (16)	8.1% (5)	
	Severe Dengue	1.6% (1)	0	
	Total	67.7% (42)	32.3% (20)	
Increased ALT (n=62)	Den. without WS	27.4% (17)	38.7% (24)	0.023
	Den. with WS	24.2% (15)	8.1% (5)	
	Severe Dengue	1.6% (1)	0	
	Total	53.2% (33)	46.8% (29)	

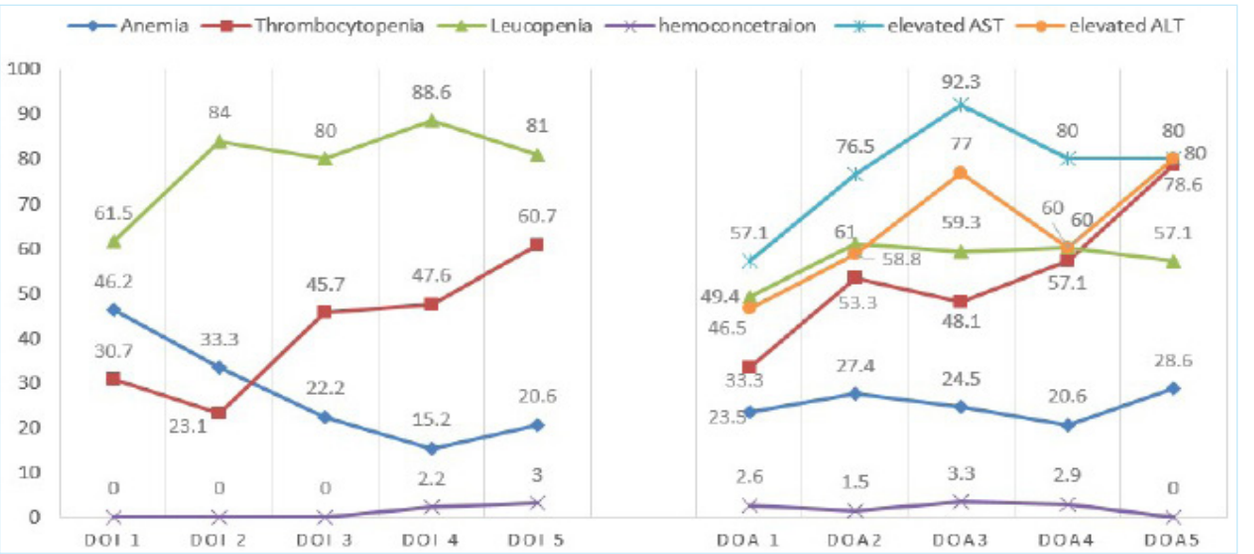

Figure 1. Hematological and biochemical parameters according to the day of admission (DOA) and day of illness (DOI).

DISCUSSION

In our study, 76% (64) were dengue without warning signs, 21.4% (18) were dengue with warning signs and 2.4% (2) were severe dengue. During the course of illness in the hospital, anemia, thrombocytopenia, hemoconcentration, and leucopenia were observed among 38.1% (32), 65.5% (55), 6% (5), and 82.1% (69) patients respectively. Elevated aspartate transaminase and alanine transaminase was observed in 67.7% (42) and 53.2% (33) patients.

In our study majority were adults, a similar majority was found in another study.[7] The mean age in our study (35.3 years) was similar to finding in other studies at 37.18 years[8] and 34.44 years.[9] Most dengue patients were adults because they belong to the working-age group and therefore may have greater exposure to insect bites. In our study pediatric patients (<15 years) constituted 7.1% which is half the number when compared to 15.7% in a previous study. [10] There is an increase in severity among the older population; among seven patients who were aged 65 years or more, one had severe dengue and four has dengue with warning signs. Severity was less among the pediatric age group (<15 years). Our study showed male predominance (53.6%, 45), like other studies from Nepal[4,5,9,11] from India[7,8] from Pakistan [12] and Africa[10] while female predominance was seen in a south Indian study.[13] Male predominance can be due to the male population, in general, being more involved in outdoor work which increases the risk of transmission of the disease, and the gender discrimination in healthcare-seeking behavior which is less among females.

NS1 is the non-structural protein of the dengue detectable during the acute phase of dengue virus infections. A positive NS1 test result is indicative of dengue infection. Dengue virus-specific IgM typically develops toward the end of the first week of illness. IgM levels are generally positive starting 4-5 days after onset of symptoms. Patients with a positive IgM test denote recent dengue virus infections.[14] In our study 90.5% (76) were NS1 antigen positive, similar findings were reported in other studies.[9,15] This suggests that most of the patients presented in the acute phase of the infection. In another study 68.33% of patients had positive NS1, 30% had positive IgM and 1.66% were positive for both.[11] Another study showed NS1 antigen positivity in 29%.[16] NS1 antigen positivity is very less in the above study when compared to 90.5% in our study.

In our study majority of cases were admitted in September, 60.7% followed by 35.7% in October while 3.6% were admitted in as late as November. A greater number of the case was reported in November in another study.[11] Significant number of cases were also reported in November and December.[12] Usually monsoon season in Nepal starts in June and ends by September. But interestingly dengue cases were not reported in early to mid-monsoon but only started to emerge and peak towards the late monsoon (September) and even towards winter months (October, November, December). This may indicate changes in the environment, vector profile, and their interaction signifying epidemiological changes.

Fever was the most common presentation,[7,10,13] likewise

97.6% of patients in our study presented with fever. In our study headaches, body ache, rashes, abdominal pain, vomiting, and bleeding was present among 77.4%, 73.8%, 21.2%, 19%, 14.3%, and 7.1% of patients respectively. [13] Similarly, symptomatology was reported in another study. [10] But a study reported body ache, headaches, vomiting, and abdominal pain only among 53%, 42%, 22%, and 10% respectively. Fever, therefore, is the most common and initial symptom. Patients living in an endemic area with fever and other suggestive symptomatology should be investigated for dengue. Retrobulbar pain was present in 48.8% of patients and was found to have a significant association with the severity of disease thus the presence of retrobulbar pain should be considered in the management of dengue patients.

In our study, bleeding manifestation was present in less number of patients (7.1%) while in other studies it was present among 24.8%[15] and 37.3% cases.[10] Though the bleeding manifestation was less in our study, there was a significant association with the severity of the disease. Therefore, a different form of bleeding manifestation should be included in inpatient history and examination among dengue patients, which may signify progression to the severity of dengue.

In our study, anemia on presentation and during the course of illness in the hospital was observed in 23.5% and 38.1% of the patients while in other studies, it was present in 44.1%[10] and 11.3% of cases.[15] Considerable prevalence of anemia was found among patients at presentation and its prevalence increased as course illness progressed during the period of hospitalization. Though there was no association found between the presence of anemia and the severity of disease, owing to the considerable prevalence of anemia, it should be considered while managing patients with dengue infection.

Hemoconcentration at presentation was observed in only 2.6% while 6% of patients developed hemoconcentration during the course of illness in the hospital. Another study reported hemoconcentration to be 23% [17], 16.6%[7], 10%[8], and 4.4%. [15] Mean hematocrit in our study was 40% which is almost equal to 39.15% in another study. [8] Though hemoconcentration was found in a less number of patients its presence in course of illness during hospitalization has a significant association with the severity of the disease. Thus, the evaluation of hemoconcentration can play a crucial role in the treatment of dengue infection.

Leucopenia was observed in many studies to be comparable to our study in 68%,[17] 70%,[13] 71.8%,[9] and 82.8%[8]. Our study reported 68.8% cases with leucopenia at presentation and that progressed to 82.1% (69) in course of illness during hospitalization. As the prevalence of leucopenia in dengue patients is high, febrile patients with leucopenia should be investigated for dengue infection, especially in an endemic region like Nepal. Also, the presence of leucopenia at presentation and during illness has a significant association with the severity of disease, it may be used as an indicator for treatment of dengue infection.

Minimum platelet counts were reported at 3,400 cells/mm^3 which is similar to the finding of 4,500 cells/mm^3.[8] In our study, 33.3% of patients had thrombocytopenia at presentation and that increased to 65.5% during the course of illness during hospitalization. A study had reported 85% of cases with thrombocytopenia and 15% had severe thrombocytopenia.[7] Thrombocytopenia as the key hematological finding was observed in 42%[13], 60% [10],69%[15], and 92%[17] in other studies which are similar or greater when compared to our study. Prevalence of thrombocytopenia is high in dengue infection, therefore any fever with thrombocytopenia should raise suspicion of dengue infection and need to be evaluated. As thrombocytopenia at presentation and in due course of illness during hospitalization was significantly associated with severity of dengue infection hence clinicians should be vigilant about this hematological parameter while treating dengue infection.

In our study, 7.7% had platelet between (50,000 to 100,000)/mm^3 and 1.3% had platelets less than 50,000/mm^3 while in another study 37.8% had platelets between (50,000 to 1 00,000)/mm^3 and 8.7% had platelets of <50,000/mm^3 in another study[9]. Levels of thrombocytopenia at presentation and in due course of illness during hospitalization had a significant association with the severity of dengue infection thus thrombocytopenia is one of the key hematological markers for clinical management of the patient and to predict severity of the disease as well.

In our study elevated AST and ALT were observed in 57% and 46.5% at presentation and 67.7% and 53.2% patients in due course of illness during hospitalization respectively. Similarly raised ALT and AST in 51.7% and 67.9% of patients respectively.[13] Overall elevated liver enzymes were elevated from 33.8%[13] to 69%.[7] Overall elevated AST and ALT are seen in dengue infection. Also, elevated ALT was significantly associated with the severity of dengue infection, thus liver enzymes especially ALT can be used as a guide for clinical management of dengue infection.

The strength of this study is that it has demonstrated clinicopathological features of patients admitted during

the dengue outbreak of 2019 in Kathmandu valley. Kathmandu valley is located at a higher altitude and the outbreak at this altitude is a new epidemiological phenomenon, thus this study generates baseline information about this epidemiological phenomenon.

The limitation is that this study was conducted among hospitalized patients only. Because of the small sample size, the findings of this study may not be generalizable to a community-level outbreak.

CONCLUSIONS

Awareness of clinicopathological features is the most important guide to proper and prompt diagnosis. The most common clinical and laboratory profiles of dengue infections could alert physicians to the likelihood of dengue virus infections. The presence of a significant association between severity of dengue and particular age group, NS1 antigen positivity, comorbidity, bleeding manifestations, retrobulbar pain, thrombocytopenia, leucopenia, and elevated ALT on presentation as well hemoconcentration, thrombocytopenia, leucopenia, and elevated ALT during illness in hospital are important findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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