

Liver Profile in Patients with Dengue Viral Infection and its Clinical Correlation

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Abstract

Background: It is well recognised that dengue fever affects several systems, occasionally leading to multi-organ dysfunction. It is known that dengue fever can cause liver involvement, and recently there have been numerous reports of fulminant hepatitis with dengue fever. This study's objective is to evaluate liver involvement in people with dengue virus infection and determine whether or not it has any bearing on prognosis.

Methods: The present study was conducted at the Department of Medicine associated with the Department of Pediatrics, Katihar Medical College and Hospital, Katihar, Bihar, from July 2021 to June 2022. There has been an increasing incidence of dengue fever in this part in recent years. Dengue fever is known to involve multiple systems sometimes resulting multi-organ dysfunction. Liver involvement is known to occur and of late there have been multiple reports of fulminant hepatitis with dengue fever.

Results: Hence the following prospective observational study in 100 consecutive patients with dengue fever was conducted to find out the profile of liver involvement in patients with dengue viral infection. The incidence of hepatic involvement in dengue fever was 85%. Among 100 cases, 48 were classical dengue fever, 41 were dengue hemorrhagic fever and 11 were dengue shock syndrome. Fever (100%), pain abdomen (73%), vomiting (68%), rash (66%) and headache (58%) were the most common symptoms, with vomiting, pain abdomen and headache being more commonly seen in patients with DHF.

Conclusion: Patients with deranged liver function tests recovered with supportive treatment.

Keywords: Hemorrhagic fever, Shock syndrome, Pain abdomen, Organ dysfunction

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Introduction

In many tropical and subtropical areas of the world, dengue is the most prevalent arboviral infection that is spread by mosquitoes and is endemic. Dengue fever prevalence has tripled during the past 50 years due to geographic growth into new

nations and, in the last ten years, a shift from urban to rural settings. Around 2.5 billion people reside in dengue-endemic areas, and an estimated 50–100 million dengue infections are reported each year. Case mortality rates range from 1% to 5%,

but they can be as low as 1% with the right care [1].

Clinically, it presents as dengue shock syndrome and dengue hemorrhagic fever in its most severe form. Over the past few years, unusual clinical dengue fever presentations have increased in frequency. Despite the fact that the liver is not a primary target organ, hepatic dysfunction is a well-known symptom, frequently accompanied by acute hepatitis, right hypochondrium discomfort, hepatomegaly, jaundice, and elevated aminotransferase levels [2-10].

Direct viral effects on liver cells or a poorly controlled host immune response to the virus can both cause liver damage as a result of dengue infection [4-12].

We definitely see a lot of patients with dengue illness, including those with unusual signs, as our hospital is a tertiary care facility. In order to determine the severity of hepatic dysfunction and its prognostic importance in patients with dengue virus infection, an assessment has been undertaken.

Material and Methods

Results

Table 1: Age wise distribution of the 100 consecutive seropositive cases of dengue fever

| Age (years) | DF (n=48) | DHF (n=52) | % |
|-------------|-----------|------------|-----------|
| 14-25 | 24(50.0%) | 25(48.1%) | 49(49.0%) |
| 26-50 | 14(29.2%) | 17(32.7%) | 31(31.0%) |
| >50 | 10(20.8%) | 10(19.2%) | 20(20.0%) |

Children are more likely to have severe dengue. Although adults might get a severe case of the illness, infants and children are more commonly affected with dengue hemorrhagic fever. The typical age range for participants in this study was between 14 and 25.

Table 2: Sex distribution of 100 serologically confirmed dengue fever cases in the present study

| Sex | DF (n=48) | DHF (n=52) | % |
|--------|-----------|------------|-----|
| Male | 27(56.2%) | 23(44.2%) | 50% |
| Female | 21(43.8%) | 29(55.8%) | 50% |

The present prospective observational study was conducted at the Department of Medicine, Katihar Medical College and Hospital, Katihar, Bihar. All serum-positive dengue patients were admitted to the hospitals from July 2021 to June 2022. A total of 100 consecutive patients with dengue fever was conducted to find out the profile of liver involvement in patients with dengue viral infection and his/her signs and symptoms of dengue fever were also positive for dengue IgM in the blood were included in the study.

Who's patients their IgM negative dengue like illnesses, Patients aged < 14 years of age, Patients with pre-existing liver diseases, and patients who refuse to be included in the study were excluded. All patients included in the study will be investigated for complete blood counts, and serum dengue IgM or IgG antibodies. Liver function tests namely serum total bilirubin, total protein, serum albumin, serum globulin, aspartate transaminase, alanine transaminase, alkaline phosphatase, prothrombin index, activated partial thromboplastin time, bleeding time, clotting time was done.

In the current study, there were 50% men and 50% women. There were exactly as many men as women. Both men and women experienced the same effects. There was a marginally higher incidence of dengue hemorrhagic fever in girls than in males, albeit this difference was not statistically significant.

Table 3: Clinical classification of 100 consecutive seropositive dengue fever cases admitted during the study period.

| No. of cases | DF | DHF |
|--------------|----|-----|
| | 48 | 52 |

Dengue is a single clinical entity that can appear in various ways and frequently has unpredictable clinical development and outcome. The incidence of DHF in our study was 52%, with 52 patients showing signs of hemorrhagic tendencies out of 100 dengue fever cases investigated. 11 cases of Grade III or IV DHF, or DSS, out of 52 DHF patients.

Table 4: Various symptoms observed in 100 patients during the study period.

| Symptoms | Total 100 cases n=100(%) |
|--------------|--------------------------|
| Fever | 100(100%) |
| Headache | 58(58%) |
| Vomiting | 68(68%) |
| Pain abdomen | 73(73%) |
| Arthralgia | 19(19%) |
| Malena | 14(14%) |
| Rash | 66(66%) |

The clinical progression and outcome of dengue, systemic and dynamic disease with a wide range of clinical manifestations ranging from mild to severe, may be highly unpredictable. Infections with the dengue virus can be asymptomatic or result in undifferentiated fever, DF, or DHF/DSS. A maculopapular rash may occasionally accompany an undifferentiated febrile illness that often affects young children. A moderate febrile syndrome or the characteristic dengue fever, which includes fever, headache, myalgias, arthralgia, and rash, may occur in older children and adults. 100% of patients had fever upon presentation. In 73% of our cases, the second most frequent complaint was abdominal pain. In 68% of the instances, there was vomiting, followed by rash in 66% of the cases and headache in 58% of patients. Less frequently occurring, occurring in 19% and 14% of cases, respectively, were arthralgia and Malena.

Table 5: Various symptoms in 2 study groups i.e. classical dengue fever (DF) Vs dengue hemorrhagic fever (DHF).

| Symptoms | DF n=48(%) | DHF n=52(%) | P-value |
|--------------|------------|-------------|----------|
| Fever | 48(100%) | 52(100%) | |
| Headache | 22(45.8%) | 36(69.2%) | 0.01(S) |
| Vomiting | 26(54.2%) | 42(80.8%) | 0.01(S) |
| Pain abdomen | 28(58.3%) | 45(86.5%) | 0.01(S) |
| Arthralgia | 6(12.5%) | 13(25%) | 0.11(NS) |
| Malena | 2(4.2%) | 12(23.1%) | 0.01(S) |
| Rash | 28(58.3%) | 38(73.1%) | 0.12(NS) |

All instances of dengue and dengue hemorrhagic fever included fever. Those with dengue

hemorrhagic fever were more likely to experience headache, vomiting, abdominal discomfort, and malaise than patients with dengue fever, which was statistically significant with p values <0.05.

Table 6: Various signs observed in consecutive seropositive 100 cases of dengue fever.

| Signs | Total cases n=100(%) |
|-----------------|----------------------|
| Edema | 32(32%) |
| Lymphadenopathy | 87(87%) |
| Petechiae | 62(62%) |
| Icterus | 24(24%) |
| Hepatomegaly | 97(97%) |
| Splenomegaly | 49(49%) |

Asymptomatic dengue infections can also manifest as undifferentiated viral syndromes, dengue fever, or DHF. The accuracy of the diagnosis of DF, DHF/DSS will be considerably improved by careful patient observation for indications of dengue fever or vascular collapse.

The majority of patients (97%) exhibited hepatomegaly, which was followed by lymphadenopathy, petechiae, splenomegaly, and icterus, which were present in 87%, 62%, 49%, and 24% of cases, respectively. In all, 32% of the cases had edoema.

Table 7: Various signs in classical dengue (DF) and dengue hemorrhagic fever (DHF).

| Signs | DF n=48(%) | DHF n=52(%) | P-value |
|-----------------|------------|-------------|----------|
| Edema | 12(25%) | 20(38.5%) | 0.15(NS) |
| Lymphadenopathy | 43(89.6%) | 44(84.6%) | 0.46(NS) |
| Petechiae | 24(50%) | 38(73.1%) | 0.01(S) |
| Icterus | 2(4.2%) | 22(42.3%) | 0.00(HS) |
| Hepatomegaly | 46(95.8%) | 51(98.1%) | 0.51(NS) |
| Splenomegaly | 18(37.5%) | 31(59.6%) | 0.02(S) |

Patients with dengue hemorrhagic fever had significantly higher rates of petechiae (73.1%), splenomegaly (59.6%), and icterus (42.3%) compared to those with dengue fever (p-value <0.05).

Patients with DHF (98.1%) tended to have hepatomegaly more frequently than those with DF (95.8%). Both groups at the presentation had edoema.

Table 8: Various laboratory parameters observed in the study of 100 consecutive cases of serologically confirmed dengue fever.

| Measurement | Mean | SD | Range | | DF/DHF n=100(%) |
|-----------------|-------|-------|-------|--------|-----------------|
| | | | Min | Max | |
| Hb | 9.74 | 2.21 | 3.2 | 14.3 | 84(84%) |
| HCT | 30.26 | 6.81 | 13.0 | 43.5 | 77(77%) |
| Platelet | 1.76 | 6.53 | 0.2 | 66.0 | 79(79%) |
| Total bilirubin | 1.65 | 1.81 | 0.5 | 8.0 | 24(24%) |
| Sr.proteins | 6.05 | 0.96 | 3.3 | 8.7 | 43(43%) |
| Albumin | 2.93 | 0.56 | 2.0 | 4.1 | 79(79%) |
| AST | 382.0 | 939.1 | 16.0 | 6758.0 | 85(85%) |

| | | | | | |
|------------------|-------|-------|------|--------|---------|
| ALT | 240.6 | 571.1 | 15.0 | 3479.0 | 71(71%) |
| Alk. phosphatase | 275.0 | 243.3 | 34.0 | 2062.0 | 81(81%) |
| PT | 39.8 | 55.1 | 13.0 | 180.0 | 80(80%) |
| APTT | 56.78 | 49.17 | 28.0 | 180.0 | 45(45%) |
| INR | 1.54 | 0.65 | 1.0 | 6.3 | 68(68%) |
| BT | 4.57 | 0.65 | 2.3 | 6.5 | 8(8%) |
| CT | 2.50 | 0.45 | 2.0 | 5.0 | 10(10%) |

At presentation, the mean values for haemoglobin, hematocrit, and platelet counts were 9.74 g/dl, 30.26, and 1.76 lakh, respectively. The average levels of total bilirubin, albumin, AST, ALT, and alkaline phosphatase were 1.65 g/dl, 2.93 g/dl, 382 uL, 240.6 uL, and 275 uL, respectively. The average PT, aPTT, INR, BT, and CT were respectively 39.8, 56.78 s, 1.54, 4.57 minutes, and 2.50 minutes.

Table 9: Various biochemical liver parameters between classical dengue fever and dengue hemorrhagic fever.

| Measurement | DF | | DHF | | DF v/s DHF | |
|-----------------|-------|-------|--------|---------|------------|----------|
| | Mean | SD | Mean | SD | t value* | P -value |
| Total bilirubin | 0.79 | 0.67 | 2.45 | 2.15 | -5.14 | 0.00(HS) |
| Direct | 0.28 | 0.59 | 1.47 | 1.64 | -4.79 | 0.00(HS) |
| Indirect | 0.51 | 0.13 | 1.00 | 0.74 | -4.49 | 0.00(HS) |
| Sr.proteins | 6.30 | 0.83 | 5.82 | 1.02 | 2.58 | 0.01(S) |
| Albumin | 3.17 | 0.52 | 2.70 | 0.51 | 4.59 | 0.00(HS) |
| AST | 117.6 | 124.6 | 626.04 | 1253.50 | -2.80 | 0.01(S) |
| ALT | 76.4 | 61.4 | 392.10 | 762.14 | -2.86 | 0.01(S) |
| Alk.phosphatase | 181.5 | 95.8 | 361.31 | 301.09 | -3.96 | 0.00(HS) |

* Unpaired t-test

Both patients with DF and DHF had abnormal results for all the liver function tests (total bilirubin, direct and indirect bilirubin, sr. proteins and albumin, AST, ALT, and alkaline phosphatase), though the degree of abnormality in DHF was much higher than in DF. With a p-value of 0.00, the derangements in total bilirubin, direct and indirect bilirubin, albumin, and alkaline phosphatase were all very significant. With p values <0.05, enzyme levels were considerably higher in DHF compared to DF.

Table 10: The various coagulation parameters in patients with DF and DHF.

| Measurement | DF | | DHF | | DF v/s DHF | |
|-------------|-------|------|-------|-------|------------|----------|
| | Mean | SD | Mean | SD | t value * | P value |
| PT | 16.6 | 7.9 | 61.10 | 69.80 | -4.39 | 0.00(HS) |
| APTT | 35.82 | 7.99 | 76.12 | 61.96 | -4.47 | 0.00(HS) |
| INR | 1.43 | 0.74 | 1.68 | 0.49 | -1.85 | 0.07(NS) |
| BT | 4.39 | 0.54 | 4.73 | 0.71 | -2.71 | 0.01(S) |
| CT | 2.43 | 0.47 | 2.57 | 0.42 | -1.49 | 0.14(NS) |

* Unpaired t-test

With a P value of <0.05, the DHF group's mean Prothrombin time (PT), mean Activated Partial Thromboplastin Time (APTT), and mean Bleeding Time (BT) were all substantially higher than those of the DF group. Regarding mean INR and clotting time values with p values >0.05, little

statistical significance was seen.

Table 11: Grading of AST and comparison between classical dengue fever and dengue hemorrhagic fever

| AST | GRADES | DF | DHF |
|-----------------|---------|------|------|
| <40 (n) | Grade A | 22.9 | 3.8 |
| 40-120 (1-3)n | Grade B | 41.7 | 28.8 |
| 120-400 (4-10)n | Grade C | 33.3 | 42.3 |
| >400 (>10n) | Grade D | 2.1 | 25.0 |

Based on AST levels during the infection period, the degree of AST level elevation was assessed and divided into four groups. Patients in Grade A had normal AST values. Patients in the Grade B group had an AST level that was not more than three times the normal amount. Patients were categorised as Grade C when their AST levels were between three and ten times the standard values. Patients were categorised as Grade D patients if their AST levels were raised by more than ten times the normal levels. Patients with DHF exhibited higher levels of AST derangements than DF patients, which is statistically extremely significant with p values of 0.00.

Table 12: Grading of AST and comparison between dengue and dengue hemorrhagic fever

| ALT | DF | DHF |
|---------|------|------|
| <40 | 33.3 | 21.2 |
| 40-120 | 45.8 | 28.8 |
| 120-400 | 20.8 | 34.6 |
| >400 | 0 | 15.4 |

According to the ALT levels during the infection, the degree of ALT level elevation was assessed and divided into four groups. Patients in Grade A had normal ALT levels. The patients in Grade B had an ALT level that was not more than three times the normal value. Patients were categorised as Grade C when their ALT readings were between three and ten times the reference norms. Patients were categorised as Grade D patients if their ALT levels were increased by more than ten times the normal levels. It is statistically significant that patients with DHF had higher levels of ALT than patients with DF.

Table 13: Grading and comparison of alkaline phosphatase levels in DF and DHF

| Alkaline Phosphatase | DF | DHF |
|----------------------|------|------|
| <125 | 27.1 | 11.5 |
| 125-250 | 60.4 | 25.0 |
| >250 | 12.5 | 63.5 |

Those with dengue hemorrhagic fever (DHF) had higher levels of alkaline phosphatase than patients with dengue fever, which is statistically significant ($p < 0.05$).

Table 14: Grading and comparison of sr. albumin levels in DF and DHF

| Sr. Albumin | DF | DHF |
|-------------|------|------|
| 2.0-2.4 | 10.4 | 34.6 |
| 2.5-2.9 | 14.6 | 32.7 |
| 3.0-3.4 | 37.5 | 26.9 |
| >3.5 | 37.5 | 5.8 |

Patients with dengue hemorrhagic fever had significantly lower levels of Serum albumin compared to patients with dengue fever.

Discussion

Serious clinical signs of dengue infection include DHF and DSS. DHF was prevalent in our sample at a rate of 52%. 11 cases of Grade III or IV DHF, or DSS, out of 52 DHF patients. Compared to studies conducted by Itha S and Chhina S *et al*, where the incidence was 33% and 18.7%, respectively, the incidence of DHF is marginally greater. This can be explained by the fact that there are more children with DHF and DSS in our institutions because they are tertiary care referral facilities.

Infections with the dengue virus can be asymptomatic or result in undifferentiated fever, DF, or DHF/DSS. A maculopapular rash may occasionally accompany an undifferentiated febrile illness that often affects young children. Both the mild febrile illness and the classic dengue fever, which include fever, headache, myalgias, arthralgia, and rash, can occur in older children and adults.

In our study, fever was the most frequent presenting symptom in patients with DF and DHF (100%). The findings were in line with those of other studies [13-18]. This may be explained by the fact that the first symptom for which the majority of parents seek medical attention is fever.

97% of cases had hepatomegaly, which is comparable to the study by Narayanappa *et al* [19,20], which had a 90% incidence. An incidence of 70–80% was found in earlier research. Although abnormal liver function tests or disease severity do not correlate with liver size, an enlarged liver is seen more frequently in the DHF group compared to the DF group. Although there were more DHF patients with hepatomegaly than in the DF group (95.8% vs. 98.1% vs. 51/52;

$p>0.05$), the difference was not statistically significant. The hepatic involvement may be caused by a direct dengue virus infection, immune-mediated hepatocyte injury, or a number of additional pathways, as previously noted [15-25].

In cases of dengue fever, abdominal pain may result from mesenteric lymphadenitis, hepatic enlargement, or subsequent shock-induced intestinal wall ischemia. Patients with DHF had abdominal pain more frequently than DF patients ($P 0.05$). When compared to other investigations, which showed an incidence of 40 to 50% [11], our cases exhibited a somewhat greater incidence of abdominal pain (73%). This may be because of the patient's advanced age, the high number of DHF cases we observed in our study, variations in the host immune system, or it may be because the circulating dengue virus in this region of the country prefers the gastrointestinal tract; further research is needed to confirm this.

Vomiting brought on by dengue fever can be brought on by intestinal wall ischemia, mesenteric adenitis, or hepatic involvement. Vomiting was evident in 68% of cases, and patients with DHF had considerably more of it than those with DF ($P 0.05$). The results were comparable to those of other research with incidences between 55 and 65% [14,19,20].

Headache was experienced by 58% of our patients, which was statistically significant ($p 0.05$) and more frequently in patients with DHF and DF. The results are comparable to those of other research with incidences between 50 and 65 percent [21-23].

Rash was observed in 66% of the cases, which is consistent with another research by Faududdin *et al.* [18] and Saba Ahmed *et al.* [17].

Splenomegaly was observed in 49% of the cases, which is slightly more than the

incidence of 20 to 35% described in other studies [15,19,20]. Patients with DHF had a higher prevalence of splenomegaly than those in the DF group ($p < 0.05$). In 32% of the instances, edoema was visible. A 40–45% incidence has been reported in other studies [14,19].

At presentation, the average haemoglobin level was 9.74 g/dl. The mean haemoglobin in other research ranged from 10.8 to 13.7 g/dl. [4,15]. The increased incidence of DHF cases in the current study may potentially be related to these low haemoglobin levels.

Patients with dengue infection frequently have abnormal liver functioning as a result of the virus directly attacking liver cells or an uncontrolled host immunological response to the virus [4].

In our research, we discovered that people with dengue infections often had abnormal liver functioning. In our study, 85% of patients had raised AST levels and nearly 71% of patients had hepatitis (elevated ALT levels).

The average amount of total bilirubin was 1.65 g/dl, which is consistent with a study conducted by Wong M *et al* [7]. 0.8 to 0.93 g/dl of mean total bilirubin was found in other studies [2,4]. When compared to the mean albumin level of 3.2 g/dl published by Chhina RS *et al* [2], the mean albumin level was 2.93 g/dl, which is slightly low.

The average levels of AST and ALT were 240.6 U/L and 382.0 U/L, respectively. The average AST value was much greater than the average ALT value, which is consistent with earlier investigations [2,4,6,10]. The pattern of viral hepatitis, whose exact cause is unknown, differs from this. It has been proposed that it might be caused by an excessive release of AST from monocytes that have been damaged by dengue infection [2, 3,12].

In comparison to past studies [4], the mean PT and aPTT values were greater at 39.8

and 56.78, respectively. With a P value of < 0.05 , the DHF group's mean Prothrombin time (PT), mean Activated Partial Thromboplastin Time (APTT), and mean Bleeding Time (BT) were all substantially higher than those of the DF group. In order to predict liver involvement or severe disease, bleeding time might therefore be utilised as a bedside technique. We presume that either a more virulent strain of dengue infection or a more hepatotoxic strain of the virus is to blame for the prolonged PT, aPTT, and BT values in our study.

Patients with DHF as opposed to DF showed AST levels that were more than three times the usual value (grades C and D). In our investigation, abnormal AST and ALT levels were found in 85% and 71% of the patients, respectively. In our investigation, the mean, the lowest, and the highest AST values were 382, 16, and 6578 units, respectively. In our investigation, the mean, minimum, and maximum ALT readings were 240. 6, 15, and 3479 units, respectively. Earlier research by Souza LJ *et al*. [6], and Souza LJ *et al*. [8], revealed a comparable pattern. This differs from the pattern in viral hepatitis, the exact cause of which is uncertain. It has been suggested that it may be due to excess release of AST from damaged monocytes during dengue infection [2,3,12]

Those with dengue hemorrhagic fever (DHF) had higher levels of alkaline phosphatase than patients with dengue fever, which is statistically significant ($p < 0.05$). According to earlier studies [6,8] which are consistent with our study, liver involvement resulted from an inflammatory process in the parenchyma triggered either directly or indirectly by the virus. This process reduced the diameter of the biliary canaliculus' lumen, caused obstruction, and resulted in bilirubinemia, jaundice, and elevated alkaline phosphatase levels.

In our study, the death rate was 4% and all 4

patients exhibited abnormal liver tests, an increased alkaline phosphatase, a low platelet count, and low blood albumin levels (2.6 g/dl). Only 2 of the 4 patients had liver enzyme levels that were 10 times (grade D) above normal, and 3 of the patients had INR values that were greater than 1.5. With supportive care, all other patients who had abnormal liver function tests recovered, which is consistent with past research [2,4].

Conclusion

100 cases were involved, of which 48 had conventional dengue fever, 41 had dengue hemorrhagic fever, and 11 had dengue shock syndrome. 50 percent of these patients were female. 49 percent of the kids were between the ages of 5 and 9. The most prevalent symptoms were fever (100%), abdominal pain (73%), vomiting (68%) rash (66%) and headache (58%) In 14% of patients, there were bleeding symptoms. The most prevalent symptoms were hepatomegaly (97%), splenomegaly (49%), and edoema (32%). Patients with dengue hemorrhagic fever had higher rates of petechiae and icterus than those with dengue fever.

In 79% of the cases, thrombocytopenia was observed, and the average haemoglobin level was 9.74 g/dl. In 24% of the cases, the level of bilirubin was abnormal, which was more common in individuals with dengue hemorrhagic fever. The average serum albumin level was 2.93 g/dl, while 43% of the patients had lower values. In individuals with DF and DHF, elevated AST (85%), ALT (71%) and alkaline phosphatase (81%) were frequently observed. Patients with severe dengue hemorrhagic fever had a higher prevalence of enzyme increase. In 80% and 45% of patients with DF and DHF, respectively, PT and aPTT were extended.

Both patients with DF and DHF had abnormal results for all the liver function tests (total bilirubin, direct and indirect bilirubin, sr. proteins and albumin, AST, ALT, and alkaline phosphatase), though the

degree of abnormality in DHF was much higher than in DF.

Out of 100 instances, alterations in liver function were found in 85 of them, and four of them resulted in death. With supportive care, all other patients with abnormal liver function tests made a full recovery.

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