

RESEARCH ARTICLE

# Acute Pancreatitis Complicating Dengue Fever – A Retrospective Observational Study

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## ABSTRACT

**Background and objectives:** This study, conducted in South India, aims to investigate the occurrence of acute pancreatitis as a complication of dengue fever and to determine the mortality rate and risk factors in patients who developed acute pancreatitis. **Subjects and Methods:** By analyzing medical records from Yashoda Hospital, Secunderabad, the incidence, mortality rate, and associated risk factors of acute pancreatitis in dengue patients were assessed. The diagnosis of acute pancreatitis was based on the revised Atlanta criteria. Statistical analyses included Chi-square and Fisher's exact tests, with a significance level set at  $p < 0.05$ . **Results:** A total of 702 dengue patients with an average age of 28.7 years were included. The severity of infection was categorized as dengue fever, dengue hemorrhagic fever, and dengue shock syndrome in 42.16%, 55.55%, and 2.28% of cases, respectively. Common dengue symptoms were fever, chills, weakness, vomiting, and body pain, while laboratory markers such as thrombocytopenia, leukopenia, elevated transaminase levels (SGPT, SGOT), and low serum albumin levels indicated complications. **Conclusion:** Acute pancreatitis was identified in 41 (5.8%) dengue patients, with a mortality rate of 1.7% in the overall population and 7.31% in those with acute pancreatitis. Notably, individuals aged 51 years or older were at higher risk for acute pancreatitis. In conclusion, this study suggests that acute pancreatitis is an underreported complication of dengue and its occurrence significantly correlates with increased mortality.

## INTRODUCTION

Dengue, an infectious disease caused by the dengue virus (DENV) and transmitted by *Aedes aegypti* mosquitoes, which primarily thrive in tropical regions around the globe. Its prevalence is intricately linked to climatic factors such as rainfall, temperature, relative humidity, as well as the unchecked expansion of urban areas. Over the past two decades, the incidence of dengue has undergone a staggering surge on a global scale, as evident from an eightfold rise in reported cases documented by the World Health Organization (WHO). This concerning trend is not restricted to any one corner of the world; rather, it is a shared predicament faced by numerous nations. While dengue casts its shadow over 129 countries, it's Asia that

bears the brunt of the burden, accounting for nearly 70% of reported infections [1].

In an effort to unravel the impact of DENV infection in India, a comprehensive community-based survey was meticulously conducted. This survey meticulously selected 240 clusters, encompassing both rural and urban areas across 15 Indian states. The regions represented a diverse cross-section of the country's geographical landscape. The study involved an extensive pool of 12,300 subjects.

The outcomes of this study unveiled a striking revelation: the seroprevalence of DENV infection in India stands at an alarming 48.7%. Notably, this prevalence escalates with advancing age, as discerned from the data presented in [Table 1] [2]. This underscores the pervasive nature of the disease and emphasizes the critical role of age as a contributing factor to susceptibility. In summary, the intricate interplay of factors including climate, urbanization, and population dynamics contribute to the widespread propagation of dengue virus. The escalating incidence rates are a poignant reminder of the urgent need for enhanced preventive measures and intensified research to stem the tide of this burgeoning health crisis.

Following an incubation period, the disease starts suddenly and goes through three phases: febrile, critical,

**Received** 29-Sep-2023 Manuscript No IPP-23-17846 **Editor Assigned** 2-Oct-2023 PreQC No IPP-23-17846(PQ) **Reviewed** 17-Oct-2023 QC No IPP-23-17846 **Revised** 23-Oct-2023 Manuscript No IPP-23-17846(R) **Published** 30-Oct-2023 DOI 10.35841/1590-8577-24.5.824

**Key words:** Dengue, Thrombocytopenia, leucopenia, serum lipase, serum amylase, mortality, DHF, DSS.

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and recovery [3, 4]. Patients who contract DENV might not show symptoms, or they could exhibit either the typical Dengue Fever (DF) or the more severe types, namely Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [3]. Due to the challenges linked to the WHO's dengue classification [as depicted in Table 2] [4], the Indian national guidelines have put forth a more practical classification (as shown in Figure 1). This new classification is easier to apply in a clinical setting and serves as a useful tool for patient treatment. In addition to the typical dengue symptoms (fever with low platelet count, sometimes with signs of plasma leakage), there have been instances of uncommon manifestations resulting from severe organ involvement, known as the expanded dengue syndrome (illustrated in Figure 1) [5]. Such organ involvement is more prevalent among individuals with existing health conditions and co-infections [6].

Acute pancreatitis as a rare complication of dengue has been documented in various sources [6, 7]. Although anecdotal reports have linked dengue with acute pancreatitis [6, 7], a study by Setiawan et al. encompassing 142 children highlighted pancreas involvement in DHF. The study found an enlarged pancreas in 29% of patients, coupled with elevated levels of serum amylase and lipase [6, 7, 8]. Another study involving 71 adult DHF patients

observed elevated serum lipase levels in 14 patients, with three patients (4.2%) being diagnosed with pancreatitis marked by serum lipase levels exceeding three times the upper limit of normal. Notably, diabetes mellitus emerged as an independent risk factor for hyperlipasemia in adult DHF patients [9].

Since there is limited information available about the occurrence, clinical features, and outcomes of acute pancreatitis in individuals with dengue fever in India, a retrospective observational study was conducted. The goal of this present study was to evaluate the frequency of acute pancreatitis and the mortality rate associated with it among dengue patients.

### MATERIALS AND METHODS

This retrospective observational study was conducted at Yashoda Hospital, a tertiary care facility in Secunderabad, India between September and December 2019. The study, approved by the hospital's Scientific Committee, focused on patients admitted with dengue fever.

Inclusion criteria involved patients over 2 months old exhibiting dengue symptoms, such as fever, arthralgia, myalgia, and generalized weakness, with or without signs of acute pancreatitis (e.g., upper abdominal pain

**Table 1.** Age-related increase in prevalence of dengue in Indiaa (aAdapted from reference [2]).

Age group (years)	Seroprevalence (%)	95% Confidence Interval
5-8	28.3	21.5-36.2
9-17	41.0	32.4-50.1
18-45	56.2	49.0-63.1
Overall	48.7%	43.5-54.0

**Table 2.** WHO classification of dengue infections and grading of severity of DHF [4].

DF/ DHF	Grade	Signs and Symptoms	Laboratory parameters
DF		✓ <b>Fever with two of the following:</b> <ul style="list-style-type: none"> <li>• Headache</li> <li>• Retro-orbital pain</li> <li>• Myalgia</li> <li>• Arthralgia / bonepain</li> <li>• Rash</li> <li>• Hemorrhagic manifestations</li> </ul> ✓ <b>No evidence of plasma leakage</b>	<ul style="list-style-type: none"> <li>• Leucopenia (WBC ≤5000 cells/mm3)</li> <li>• Thrombocytopenia (platelet count &lt;150,000 cells/mm3)</li> <li>• Rising hematocrit (5-10%)</li> <li>• No evidence of plasma loss</li> </ul>
DHF	I	✓ <b>Fever and hemorrhagic manifestation</b> (positive tourniquet test) and ✓ <b>Evidence of plasma leakage</b>	<ul style="list-style-type: none"> <li>• Thrombocytopenia (platelets &lt;100,000 cells/mm3)</li> <li>• Hematocrit rise ≥20%</li> </ul>
DHF	II	As in Grade I plus spontaneous bleeding	<ul style="list-style-type: none"> <li>• Thrombocytopenia (platelets &lt;100,000 cells/mm3)</li> <li>• Hematocrit rise ≥20%</li> </ul>
DHF#	III	As in Grade I or II plus circulatory failure [weak pulse, narrow pulse pressure (≤20mmHg), hypotension, restlessness]	<ul style="list-style-type: none"> <li>• Thrombocytopenia (platelets &lt;100,000 cells/mm3)</li> <li>• Hematocrit rise ≥20%</li> </ul>
DHF#	IV	As in Grade III plus profound shock with undetectable BP and pulse	<ul style="list-style-type: none"> <li>• Thrombocytopenia (platelets &lt;100,000 cells/mm3)</li> <li>• Hematocrit rise ≥20%</li> </ul>

#DHF grade III and IV are DSS. DF: Dengue fever; DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome; WBC: White blood cell; BP: Blood pressure.

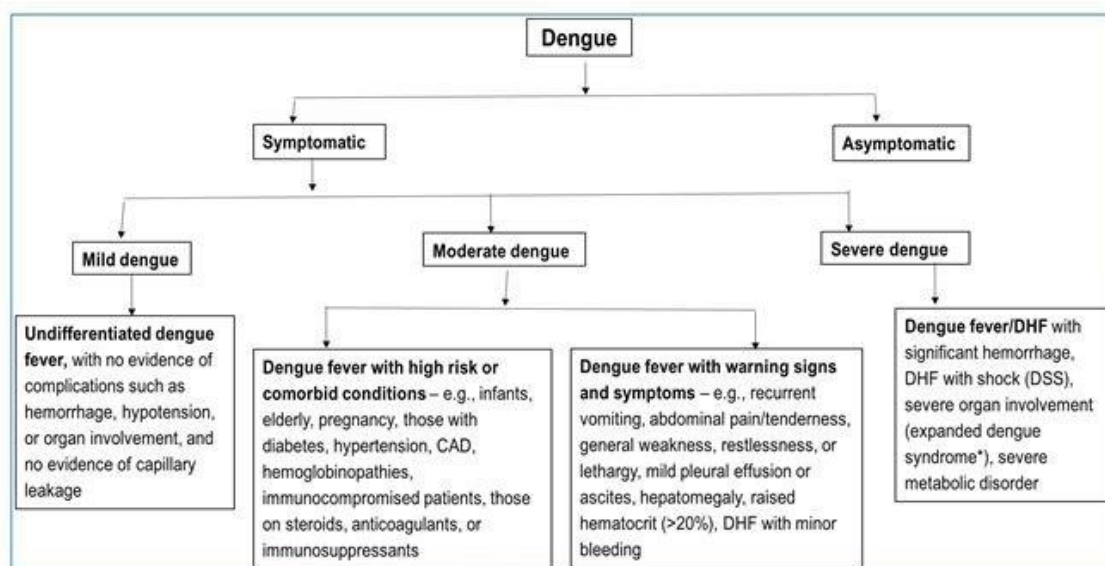


Figure 1: Classification of Dengue-Indian National Guidelines<sup>5</sup>.

\*These may involve the CNS (e.g., encephalopathy, seizure), GIT (e.g., acute hepatitis, acute pancreatitis, cholecystitis), kidneys (e.g., acute renal failure, acute tubular necrosis), heart (myocarditis, arrhythmias, pericardial effusion), lungs (e.g., pulmonary edema, ARDS, pleural effusion), or the eyes (e.g., conjunctival bleeding, macular hemorrhage, visual impairment, optic neuritis). ARDS: Acute respiratory distress syndrome; CAD: Coronary artery disease; CNS: Central nervous system; DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome.

radiating to the back). Diagnosis of dengue was confirmed using either Nonstructural Protein 1 (NS1) antigen test or dengue antibodies (IgM). Patient data, including clinical and laboratory information, were extracted from medical records. The study assessed the incidence of acute pancreatitis in dengue patients, mortality rate, and its correlation with dengue complications. Acute pancreatitis diagnosis was based on the revised Atlanta criteria, requiring the fulfillment of two or more specified criteria's (a) abdominal pain suggestive of pancreatitis; (b) serum amylase or lipase level greater than three times the upper normal value; or (c) characteristic imaging findings [10,11].

Statistical analysis was carried out using the statistical package for the social sciences (SPSS) version 24. Mean and Standard Deviation (SD) values were calculated for quantitative variables and proportions were calculated for qualitative variables. Median value with Inter Quartile Range (IQR) was calculated for skewed variables. Chi-square test and Fisher's exact test for associations were used to carry out the statistical analysis of the data and a probability (p) value of less than 0.05 was considered as the level of significance.

## RESULTS

### Baseline characteristics and presenting features

The study enrolled 702 patients ranging from 2 months to 83 years old, with an average age of 28.7 years ( $\pm$  16.32). These patients were diagnosed with dengue. The characteristics of these patients and the primary symptoms they exhibited are detailed in Table 3. The prevalent symptoms of dengue included fever, chills, weakness,

vomiting, and body pain. Among the 702 patients, 296 (42.2%) had DF, 390 (55.55%) had DHF, and 16 (2.3%) had DSS.

### Laboratory investigations

The findings from crucial laboratory tests are outlined in Table 4. In these patients, dengue infection primarily led to thrombocytopenia, leukopenia, hepatitis, and reduced serum albumin levels indicating capillary leakage [Table 4].

### Dengue-related acute pancreatitis

113 patients (16.1%) reported abdominal pain or discomfort. Among those with persistent abdominal pain, elevated serum amylase and serum lipase levels were observed. The median values (IQR) for serum amylase were 84 (61–173) U/L (normal range: 30–110 U/L), and for serum lipase, they were 377 (326–672.5) U/L (normal range: 23–300 U/L). Utilizing the revised Atlanta classification, 41 patients (5.8%) with dengue in our study were diagnosed with acute pancreatitis [Table 5].

Of the 41 dengue patients with acute pancreatitis (21 male, 20 female), 19 were diagnosed with DF, 20 with DHF, and 2 with DSS. Dengue diagnosis was confirmed using NS1 antigen tests (n = 23) and IgM (n = 18). Three patients had type 2 diabetes, and one had hypertension.

The incidence of pancreatitis was notably higher in dengue patients aged  $\geq$ 51 years (p = 0.012). An age-related linear connection was found with acute pancreatitis (p = 0.004) in dengue patients. The incidence of acute pancreatitis showed no significant associations with low platelet count (p = 0.720), hepatitis presence (p = 0.281), low albumin levels (p = 0.880), or dengue severity at presentation (p = 0.890) [Table 6].

**Table 3.** Demographic profile of the patients enrolled in the study and the major presenting symptoms of dengue (n = 702).

Baseline characteristics		Major presenting symptoms	
Parameter	No. of patients (%)	Symptom	No. of patients (%)
<b>Age (years)</b>		Fever	675 (96.15)
2M-18yrs	210 (29.9)	Chills	223 (31.77)
19-29	182 (25.9)	Cough	98 (13.96)
30-39	136 (19.3)	Vomiting	196 (27.92)
>40	174 (24.7)	Body pain	180 (25.64)
<b>Gender</b>		Joint pain	29 (4.13)
Female	272 (38.7)	Myalgia	83 (11.82)
Male	430 (61.3)	Abdominal pain / discomfort	113 (16.1)
<b>Dengue Diagnosis (Method used*)</b>		Weakness	260 (37.03)
NS1 antigen	463 (66.0)	Rash	22 (3.13)
IgM	274 (39.0)	Poor oral intake	11 (1.57)

\*NS1-ELISA: >11 PU is taken as positive. Dengue IgM-ELISA: >11 PU units is taken as positive. ELISA: Enzyme-linked immunosorbent assay; NS1: Non-structural protein 1; IgM: Immunoglobulin M; PU: Panbio units.

**Table 4.** Results of laboratory investigations of the enrolled dengue patients.

Parameter (Units)	Normal range*	N	Minimum value	Maximum value	Median (IQR)	Dengue complications [n (%) patients]
TLC (cells/ $\mu$ L)	4,000-10,000	701	233	1,66,680	4320	Leukopenia: 314 (44.8)
Platelet count <sup>a</sup> (lakhs/cc)	1.5-4.1	701	0.05	15.1	0.9801 -0.94	Leukocytosis: 79 (11.25) Thrombocytopenia: 522 (74.4)
SGOT or AST (U/L)	Male:21-72 Female: 9-52	683	16	13,211	115	Hepatitis (raised liver enzymes >1.5 times the ULN): 457 (65%)
SGPT or ALT (U/L)	Male:17-59 Female: 14-36	682	4	5,051	69	
Albumin <sup>a</sup> (g/dL)	3.5-5.1	674	0.9	6.7	3.471 -0.58	Low serum albumin denoting capillary leakage: 256 (36.46%)
Amylase (U/L)	30-110	30	61	173	84	Acute pancreatitis: 41 (5.8%)
Lipase (U/L)	23-300 U/L	66	326	672.5	377	

**Table 5:** Summary.

Total no	n = 702	Mortality	%	P Value
Pancreatitis	41	3 / 41	7.3	0.0051
Without Pancreatitis	661	9 / 661	1.36	
All cases	702	12 / 702	1.7	

**Table 6:** Age and Acute Pancreatitis.

Age (Years)	Acute Pancreatitis (%)
10-20	6 (14.6)
21-30	7 (17.0)
31-40	6 (14.6)
41-50	8 (19.5)
>51	14 (34.1)

### Clinical outcome

The study revealed a mortality rate of 1.7% (12 patients) among the entire study population. Within the subgroup of dengue patients with acute pancreatitis, the mortality rate was 7.31% (3 out of 41 patients). A noteworthy correlation was observed between the occurrence of acute pancreatitis in dengue patients and mortality, with a significance level of  $p = 0.0051$ .

### DISCUSSION

In this retrospective observational analysis involving

702 individuals with dengue, we discovered that our group's clinical signs and lab results aligned with those documented in existing literature sources [1, 3, 5]. The study identified an incidence of 5.8% for acute pancreatitis. We employed serum lipase as the primary diagnostic parameter for pancreatitis due to its superior performance compared to serum amylase [11].

The study's mortality rate among dengue patients with acute pancreatitis stood at 7.31%, underscoring the potential life-threatening nature of this complication [7].

Notably, no connection was established between acute pancreatitis and lab parameters (like thrombocytopenia or elevated serum transaminases), the development of other dengue-related complications (such as hepatitis or low serum albumin levels indicating capillary leakage), or mortality in this investigation. However, an age exceeding 51 years correlated with a higher likelihood of acute pancreatitis.

As per the World Health Organization (WHO), the term "expanded dengue syndrome" is used to describe atypical symptoms observed in dengue patients, encompassing neurological, gastrointestinal/hepatic, renal, and other organ-related issues. These gastrointestinal/hepatic symptoms consist of hepatitis/fulminant hepatic failure, acalculous cholecystitis, acute pancreatitis, hyperplasia of Peyer's patches, and acute parotitis. These complications are thought to arise from severe shock, underlying host conditions/diseases, or coinfections [4].

Acute pancreatitis is among the manifestations of expanded dengue syndrome, documented in references [4, 12, 13]. Despite being an infrequent complication of dengue, a study involving 774 patients with DHF indicated a 4.2% occurrence of acute pancreatitis, suggesting that hyperlipasemia and pancreatitis might be more common than previously believed. These conditions could be underdiagnosed complications of dengue. [9] An Indian study focusing on 520 cases of expanded dengue syndrome reported an incidence of acute pancreatitis at 12.88% [14].

While acute pancreatitis is commonly attributed to factors like gallstones and alcohol consumption, it's important to also consider infection as a potential cause, particularly in patients who are exhibiting acute pancreatitis symptoms and show signs of dengue fever. In cases where infections lead to acute pancreatitis, the diagnosis can be classified as definite when there is clear surgical or radiologic evidence of pancreatitis. Alternatively, it can be categorized as probable if there's biochemical evidence, such as serum amylase and lipase levels elevated by more than three times the Upper Limit of Normal (ULN) [15]. Furthermore, a possible diagnosis can be made even in the absence of symptoms, based solely on asymptomatic biochemical indicators. In the context of the study at hand, the diagnosis of acute pancreatitis was established by combining symptomatic abdominal pain and elevated serum amylase/lipase levels, classifying it as probable pancreatitis.

The precise pathogenic mechanisms underlying pancreatitis in the context of dengue infection remain inadequately elucidated. Current understanding suggests that pancreatitis may arise due to several plausible mechanisms. Firstly, it is postulated that direct infiltration of the pancreas by the dengue virus might trigger an inflammatory cascade, resulting in notable damage to the acinar cells. Alternatively, an autoimmune response could

be provoked in the acinar cells in response to the presence of the virus. Furthermore, the emergence of pancreatitis might also be attributed to interstitial edema affecting the ampulla of Vater, subsequently leading to an impediment in the outflow of pancreatic fluid.

This investigation holds substantial implications for clinical practice. It is worth noting that acute pancreatitis is not an infrequent complication observed in the context of dengue infection, a fact corroborated by existing literature. Importantly, our study demonstrates that such instances of pancreatitis did display a significant association with mortality. Given that patients typically initiate contact with family physicians during epidemic periods, heightened awareness regarding the potential for unconventional dengue presentations, including pancreatitis, becomes imperative. This heightened recognition is pivotal for facilitating early diagnosis and the prompt implementation of appropriate management strategies [7, 14].

## CONCLUSION

In this retrospective, observational investigation encompassing a cohort of 702 Indian individuals afflicted by dengue, an observed occurrence of acute pancreatitis manifested at a prevalence rate of 5.8%. It is worth noting that acute pancreatitis, while not an infrequent complication, might conceivably suffer from inadequate documentation within the realm of clinical practice. Furthermore, a notable correlation emerged between the occurrence of acute pancreatitis and mortality outcomes, thereby underscoring its clinical significance.

## CONFLICTS OF INTEREST

None

## FUNDING RESEARCH NA

We have taken the Ethics Committee permission from Yashoda Academy of Medical Education And Research before collecting the data : RS/PP/2020.

## ACKNOWLEDGEMENTS

We are grateful to Dr. N. Balakrishna for the statistical analysis of the data and also very thankful to Dr. Shubhasis Dan, Regional Medical Advisor, Gastroenterology, Abbott India Ltd. for his contribution towards scientific discussion and inputs.

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