Risk factors of GI bleeding resulting in decreased hematocrit and requiring blood products transfusion in patients admitted with dengue fever to tertiary care hospital

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Abstract

Aim: Study of various demographic and other variables in patients with GI bleeding can help give us an insight into the predictors of GI bleeding so it can be identified well in time and controlled before any fatal outcome.

Introduction: With a sevenfold increase in incidence during the past three decades, dengue fever, though treatable, continues to remain a major epidemic with seasonal variations associated with significant morbidity and mortality in our region. [1]

Methodology: The methodology used in this study is retrospective cohort study. The data of 400 dengue patients admitted between September 2022 to November 2022 was collected, out of which 45 patients presented with or developed GI bleeding during hospital stay, chosen by the convenient sampling technique. The relative risk of bleeding is calculated with each exposure element.

Results: Among the 455 patients, 45 patients (9.8%) presented with GI bleeding, among them 35 (77.8%) were males and 10 (22.2%) were females. The bleeding mostly started on either day 5 (26.7%) or 7 (24.4%) of onset of fever. Among the risk factors calculated, during the Leaking phase, the levels of AST and ALT (>99) and INR (>1.5) predicting previous hepatic injury or hepatitis associated with dengue were the most significant risk factors with P values 0.0003, 0.0001, 0.0001 respectively.

Conclusion: According to our study the most significant risk factor of GI bleed in dengue patients in our local population are leaking phase, hepatic dysfunction evidenced by elevated AST and ALT (>99) and INR (>1.5).

Keywords (MeSH/Cochrane Library): Dengue Fever, Dengue hemorrhagic fever, Dengue shock syndrome, Gastrointestinal hemorrhages, INR, Dengue Complications, Dengue and Gastrointestinal bleeding, Dengue Risk Factors.

Introduction

Dengue fever is a widespread viral disease transmitted by Aedes mosquito, affecting millions of people around the globe each year. It is a significant public health concern in tropical and subtropical regions, causing substantial morbidity and mortality[2]

While dengue fever primarily presents with fever, rash, headache and joint pain, severe forms of the disease can lead to life-threatening complications, including gastrointestinal bleeding. Gastrointestinal bleeding in patients with dengue fever is a serious condition that requires immediate medical attention, yet the risk factors associated with this complication remain poorly understood.[3]

Gastrointestinal bleeding is a major cause of mortality in patients with dengue fever, accounting for a significant number of deaths in severe cases. It manifests as the passage of bleed through the gastrointestinal tract, resulting in symptoms such as vomiting of blood (hematemesis), passing blood in the stool (melena), or rectal bleeding [4] .The occurrence of gastrointestinal bleeding in dengue fever patients is a complex phenomenon influenced by various factors, including viral pathogenesis, immune response, vascular integrity, co-infections and patient characteristics.[5]

This research paper aims to investigate and analyze the risk factors associated with gastrointestinal bleeding in patients with dengue fever. Understanding these factors is crucial for early identification, appropriate management, and improved outcomes in affected individuals [6]. By elucidating the underlying mechanisms and identifying significant predictors, healthcare professionals can develop targeted interventions to reduce the incidence and severity of this life-threatening complication.

Dengue fever, caused by one of the four serotypes of the dengue virus (DENV-1 to DENV-4), poses a significant health burden in endemic areas worldwide. The disease ranges from mild to severe forms, with severe dengue being characterized by plasma leakage, organ impairment, and bleeding manifestations [7]. Gastrointestinal bleeding is a particularly serious complication associated with severe dengue, contributing to increased morbidity and mortality rates.

Gastrointestinal bleeding in dengue fever is believed to result from multiple factors, including direct viral effects on the endothelial cells, immune-mediated mechanisms[8], and alterations in hemostasis. However, the precise pathogenesis and the risk factors contributing to the development of this complication remain poorly understood. Identifying these risk factors is crucial for risk stratification, early detection, and timely intervention. [9]

The primary aim of this research paper is to investigate the risk factors associated with gastrointestinal bleeding in patients with dengue fever. By conducting a comprehensive review of the available literature and analyzing relevant clinical data, this study aims to identify and evaluate the significant predictors of this life-threatening complication. The findings will contribute to a better understanding of the pathogenesis and management of gastrointestinal bleeding in dengue fever patients, ultimately improving patient outcomes and reducing mortality rates.

Methodology:

After getting approval from ethical review board of DHQ teaching hospital Gujranwala, data of dengue patients was obtained. Four hundred dengue patients were admitted from 1st September 2022 till end of November 2022. Out of these 45 patients had developed Gastrointestinal bleeding during hospital stay in form of hematemesis, Melena or both.

The sample was chosen by convenient sampling technique. The relative risk of bleeding is calculated with each exposure element. The risk factors studied are smoking, history of PPI usage, NSAID intake in the past two weeks, INR>1.5, ALT>99, AST>99, Platelet count at presentation < 100,000 and leaking phase. The relative risk for each of the variable was calculated using data in bleeding and non bleeding patients. P value for each of the risk factor was calculated and compared against other factors.

Patients with fever were screened on the dengue counter, which was made on the main entrance to the Medical emergency. Patients with fever were screened for low platelet count and low leucocyte count termed as bicytopenia. Patients having bicytopenia were further assessed for dengue fever though dengue IgM or NS1 screening. All patients who had positive dengue serology or positive NS1 were labeled as dengue patients and were shifted to dengue ward.

Within the dengue ward patients were segregated into three main groups. These groups were made on the basis of dengue disease spectrum. First group comprised of patients having features of only dengue fever, second group comprised of patients having dengue shock syndrome and third group comprised of patients having dengue hemorrhagic fever.

All patients were managed according to DEAG (Dengue Expert Advisory Group) guidelines. Patients with dengue fever were monitored four hourly, patients with dengue shock syndrome were monitored hourly and patients with dengue hemorrhagic fever were monitored half hourly [10]. On arrival all base line laboratory tests were performed . Chest X ray, Ultrasound abdomen and echocardiography was done. Shock profile was done of patients who were having either dengue shock syndrome or dengue hemorrhagic fever. Special CBC machine was made available in the dengue ward for quick Complete blood counts. CBC was done before and after every saline bolus. Patients with dengue hemorrhagic fever were sent for upper and lower gastrointestinal endoscopies to identify if any underlying cause.

Results:

Among the 455 patients, 45 patients (9.8%) presented with GI bleeding, among them 35 (77.8%) were males and 10 (22.2%) were females. The bleeding mostly started on either day 5 (26.7%) or 7 (24.4%) of onset of fever, with it starting as early as day 2 and a late as day 12. Among the risk factors calculated, during the Leaking phase, the levels of AST and ALT (>99) and INR (>1.5) predicting previous hepatic injury or hepatitis associated with dengue were the most significant risk factors with P values 0.0003, 0.0001, 0.0001 respectively.

The elevated AST, ALT and INR carry the same risk depicting the significance of liver injury either because of previous hepatic disease or hepatitis associated with dengue in predicting the risk of GI bleed. Smoking and history of PPI use (predicting risk of acid peptic disease) were also categorized as high risk factors with P values 0.0026 and 0.014 respectively.

Platelet count < 100,000/ ul on presentation conferred mild risk with P value 0.075 while NSAID intake in last 2 weeks surprisingly didn't confer any significant risk with P value 0.791.

Variable	ALT > 99	Results	
Exposed Group		Relative Risk	3.3485
Number with positive (bad) outcome	26	95% CI	1.9207 to 5.8377
Number with negative (good) outcome	206	Z Statistic	4.262
Control Group		Significance Level	P < 0.0001
Number with positive (bad) outcome	19	NNT (Harm)	7.239
Number with negative (good) outcome	204	95% CI	12.650 to 5.070
Variable	**AST > 99**	**Results**	
Exposed Group		Relative Risk	3.2098
Number with positive (bad) outcome	26	95% CI	1.8399 to 5.5994
Number with negative (good) outcome	110	Z Statistic	4.108
Control Group		Significance Level	P < 0.0001
Number with positive (bad) outcome	19	NNT (Harm)	7.598
Number with negative (good) outcome	300	95% CI	13.712 to 5.255
Variable	**Smoking**	**Results**	
Exposed Group		Relative Risk	0.014
Number with positive (bad) outcome	0	95% CI	0.0009 to 0.2258
Number with negative (good) outcome	200	Z Statistic	3.009
Control Group		Significance Level	P = 0.0026
Number with positive (bad) outcome	45	NNT(Benefit)	5.706
Number with negative (good) outcome	210	95% CI	4.377 to 8.194

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Variable	Platelets < 100	Results	
Exposed Group		Relative Risk	1.844
Number with positive (bad) outcome	35	95% CI	0.9382 to 3.6241
Number with negative (good) outcome	263	Z Statistic	1.775
Control Group		Significance Level	P = 0.0759
Number with positive (bad) outcome	10	NNT (Harm)	18.603
Number with negative (good) outcome	147	95% CI	8.989 to 267.754
Variable	INR > 1.5	**Results**	
Exposed Group		Relative Risk	12.3889
Number with positive (bad) outcome	9	95% CI	9.0575 to 16.9454
Number with negative (good) outcome	0	Z Statistic	15.75
Control Group		Significance Level	P < 0.0001
Number with positive (bad) outcome	36	NNT (Harm)	1.088
Number with negative (good) outcome	410	95% CI	1.349 to 0.911
Variable	PPI Intake	**Results**	
Exposed Group		Relative Risk	32.5878
Number with positive (bad) outcome	45	95% CI	2.0253 to 524.3409
Number with negative (good) outcome	250	Z Statistic	2.458
Control Group		Significance Level	P = 0.0140
Number with positive (bad) outcome	0	NNT (Harm)	6.711
Number with negative (good) outcome	105	95% CI	12.517 to 4.585
Variable	NSAID intake	**Results**	
Exposed Group		Relative Risk	1.1984
Number with positive (bad) outcome	2	95% CI	0.3162 to 4.5421
Number with negative (good) outcome	15	Z Statistic	0.266
Control Group		Significance Level	P = 0.7901
Number with positive (bad) outcome	43	NNT (Harm)	51.352
Number with negative (good) outcome	395	95% CI	6.094 to 7.990
Variable	leaking Phase	**Results**	
Exposed Group		Relative Risk	175.5833
Number with positive (bad) outcome	45	95% CI	10.8893 t0 2831.1693
Number with negative (good) outcome	110	Z Statistic	3.643
Control Group		Significance Level	P = 0.0003
Number with positive (bad) outcome	0	NNT (Harm)	3.448
Number with negative (good) outcome	300	95% CI	4.197 to 2.926

Discussion

Dengue fever is a significant global health concern, affecting millions of people annually. While the majority of dengue cases present with mild symptoms, some patients may experience severe manifestations, including gastrointestinal (GI) bleeding [11]. This paper aims to explore the risk factors associated with GI bleeding in patients with dengue fever. Through an extensive review of clinical data, we examine various factors that contribute to the development of GI bleeding in dengue-infected individuals. Understanding these risk factors is crucial for early identification, timely intervention and improved outcomes[12].

Elevated liver enzymes serve as a valuable marker for identifying the risk factors of GI bleeding in patients with dengue fever. Dengue virus infection can cause hepatic involvement, leading to liver damage and subsequent elevation of liver enzymes such as alanine transaminase (ALT) and aspartate transaminase (AST)[13]. Several mechanisms contribute to this phenomenon.

Firstly, the dengue virus directly infects hepatocytes, leading to hepatocellular injury and subsequent release of liver enzymes into the bloodstream. The extent of liver involvement and the severity of liver enzyme elevation can vary, and higher levels of ALT and AST have been associated with a more severe disease course[13].

Secondly, thrombocytopenia, a common feature of dengue fever, can exacerbate liver damage [14]. Reduced platelet counts impair the blood's clotting ability, leading to microhemorrhages and liver bleeding. This may contribute to the increased risk of GI bleeding observed in patients with elevated liver enzymes.

Furthermore, elevated liver enzymes may indicate the presence of coagulopathy, as the liver plays a crucial role in producing clotting factors. Impaired liver function can lead to abnormalities in coagulation system, increasing the likelihood of bleeding complications, including GI bleeding[15].

Monitoring liver function and platelet levels can aid in timely intervention and appropriate management to prevent severe bleeding episodes. Additionally, understanding the association between liver enzyme elevation and GI bleeding can help healthcare providers tailor their treatment strategies, thus improving patient outcomes and reducing the overall burden of dengue-related complications.

Smoking can be considered a marker of risk factors for gastrointestinal (GI) bleeding in patients with dengue fever [16]. Smoking has been associated with various adverse effects on the cardiovascular and respiratory systems, which can exacerbate the severity of dengue infection. In the context of dengue, smoking may lead to increased inflammation and impaired platelet function, thereby contributing to the risk of bleeding complications, including GI bleeding. Moreover, smoking-induced vascular damage may further compromise the already fragile blood vessels in dengue-infected individuals, increasing the likelihood of GI bleeding. Identifying smoking history in dengue patients can help healthcare professionals assess their bleeding risk and implement appropriate preventive measures and interventions.

Proton pump inhibitors (PPIs) intake can serve as a marker of risk factors for gastrointestinal (GI) bleeding in patients with dengue fever. PPIs are commonly prescribed medications that reduce stomach acid production and are used to treat various gastrointestinal conditions. However, in the context of dengue fever, PPI use may potentially increase the risk of GI bleed. PPIs can interfere with the normal gastric defense mechanisms, making the stomach lining more susceptible to damage from dengue-induced alterations in the coagulation system. Additionally, PPIs may mask early symptoms of GI bleeding, delaying its detection and appropriate management. Healthcare providers should be cautious in prescribing PPIs to dengue patients, especially those at higher risk of bleeding complications.[17]

NSAID (Non-steroidal Anti-Inflammatory Drug) are commonly used to manage fever and pain, but they can interfere with platelet function and disrupt the integrity of the stomach lining [18] increasing the susceptibility to GI bleeding. In the context of dengue fever, where thrombocytopenia and coagulation abnormalities are already present, NSAID use may exacerbate bleeding complications. Healthcare providers should exercise caution when prescribing NSAIDs to patients with dengue fever and consider alternative pain management strategies to reduce the risk of GI bleeding in this vulnerable population[19]

The "leaking phase" in dengue fever is one of the important marker of gastrointestinal (GI) bleeding. During the leaking phase, plasma leakage from blood vessels can lead to a decrease in blood volume, impaired kidney perfusion[20] and a drop in platelet counts, contributing to a higher risk of bleeding complications. GI bleeding is a severe manifestation that can occur in this phase due to the fragile and weakened blood vessels. Monitoring patients closely during the leaking phase is crucial to detect early signs of GI bleeding and promptly initiate appropriate interventions to improve patient outcomes and prevent life-threatening complications.

Conclusion:

According to our study the most significant risk factor of GI bleed in dengue patients in our local population are leaking phase, hepatic dysfunction evidenced by elevated AST and ALT (>99) and INR (>1.5).

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