Clinical profile and predictors of severe bleeding and mortality in dengue fever patients

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DOI: https://doi.org/10.22271/23487941.2021.v8.i2a.520

Abstract
Background: Dengue viral infection is one of the common tropical diseases spread by the bite of infected *Aedes aegypti* mosquito. Nearly 100 countries and 40% of the world population are at risk of getting dengue fever. Recent 2011 WHO classification categorized this entity into Dengue without warning signs, Dengue with warning signs, and severe dengue.

Objective: To study the clinical features, predictors of mortality, and severe bleeding of dengue fever.

Materials and Methods: This was a prospective cross-sectional study conducted in Nizams Institute of Medical Sciences, Hyderabad, India. A total of 200 patients diagnosed with dengue fever were recruited into the study from August 2018 to October 2019. Clinical features, laboratory profile and outcomes were recorded and analyzed by using SPSS software.

Results: A total of 200 patients were included in the study. Among them 118(59%) were male, 82(41%) were female. Fever was present in all 200(100%) patients. Leukocytosis was found in 30(15%) patients. Thrombocytopenia, at admission, was mild to moderate in 90(45%) and severe in 50(25%) patients. Abnormal PT (Prothrombin Time), aPTT was seen in 20(10%) and 80(40%) patients respectively. Hypoalbuminemia (<3.5 g/dl) was seen in 84(42%) patients of the total group with the mean value of 2.8± g/dl.

Conclusion: Fever was the universal symptom while rash was the commonest sign. Predictors of severe bleeding were: Mean platelet count at admission, Serum albumin, and Prolonged aPTT and predictors of mortality were: Female sex, Mean hemoglobin, Mean TLC, and Mean albumin.

Keywords: dengue fever, clinical profile, severe bleeding, mortality

Introduction
Dengue, a neglected tropical disease, also known as “break-bone fever” was described in 1780 by Benjamin Rush. Worldwide nearly 2.5 billion people continue to live at risk of contracting the infection while 50 million cases and 20,000 deaths are estimated to occur in 100 endemic countries. Treated Dengue hemorrhagic fever (DHF)/Dengue shock syndrome (DSS) is associated with a 1% mortality rate while the mortality rate among untreated cases escalates to 20%. A recent disease distribution model estimated there were 390 million DENV infections in 2010, including 96 million apparent infections (i.e., cases that manifest at any level of clinical or subclinical severity). Overall, 70% of these apparent infections occurred in Asia [1] while the Southeast Asian region together with the Western Pacific region bears nearly 75% of the current global disease burden with 50 million cases of dengue infection and 300,000 cases of dengue hemorrhagic fever occurring in Asian countries [3].

Dengue fever (DF) is an arthropod-borne viral fever. Estimates suggest that India is one of the seven identified countries in the South-East Asia region regularly reporting the incidence of DF/DHF outbreaks and may soon transform into a major niche for dengue infection. Dengue infections vary in severity, ranging from influenza-like self-limiting illness to life-threatening severe dengue (Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)) which if left untreated, are associated with a case fatality rate of 5% [2]. Although the mortality rate for dengue cases is low, even uncomplicated dengue fever causes considerable suffering and loss of productivity despite its short duration. The various manifestations of dengue may not have a distinct line of demarcation. With this background, we aimed to study the clinical profile of dengue patients and the objectives are to study the prognostic factors of severe bleeding and outcome.
Methods
This study is a prospective, cross-sectional observational study conducted from August 2018 to October 2019 at Nizam’s Institute of Medical Sciences, a tertiary care hospital in Hyderabad, Telangana state, India. A total of 200 patients with symptoms suggestive of Dengue fever and confirmed with dengue NS1 antigen, IgM, or ELISA were included after taking informed consent. Patients with other identified causes for their symptoms like malaria, enteric fever, meningitis, sepsis, or infection elsewhere, and those with chronic liver disease, chronic kidney disease, and other chronic diseases affecting the renal, liver, and hematological parameters and those who have not given consent were excluded. All patients with symptoms suggestive of dengue were tested with an immunochromatographic one-step assay (SD BIOLINE Dengue Duo Rapid Test®). This is a rapid test that detects the presence of NS1 antigen, IgM, as well as IgG antibodies, and results can be interpreted within 15-20 minutes. The sensitivity of the test is 92.4% and the specificity is reported to be approximately 98.4%. Routine laboratory profiles of all patients were determined using an automated counter, Beckman Coulter's five-part hematology analyzer with reticulocyte count (HMX model). If the platelet count was found to be less than 1 lakh/mm³, reconfirmation with microscopy under oil immersion was done. Statistical analysis was done by using SPSS (Software Package used for Statistical Analysis) version 17.0 software. Continuous variables were presented as mean and Standard Deviation (SD). Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using the Chi-squared test after the construction of the 2x2 table. For numeric variables, a student’s t-test was used to find the difference between Dengue fever and severe dengue, for all statistical tests, a “p-value” less than 0.05 was taken to indicate a significant difference.

Results
A total of 200 patients were included in the study. Among them 118 (59%) were male, 82 (41%) were female. Patients were classified according to WHO 2009 classification system (WHO [5]) into three grades based on the level of severity, as Dengue without Warning Signs, Dengue with Warning Signs, and Severe Dengue, and the data is analyzed accordingly. The number of patients in each group was 22 (11%), 62 (31%), 116 (58%) in DF, DF with Warning Signs and severe Dengue respectively.

Table 1:  Demographic characteristics of the Patients with dengue infection.

|                     | Total | DF without warning signs | Dengue with warning signs | Severe Dengue |
|---------------------|-------|--------------------------|--------------------------|--------------|
| No. Of patients     | 200   | 22(11%)                  | 62(31%)                  | 116(58%)     |
| Male/ Female        | 118(59%)/ 82(41%) | 10(45%)/ 12(55%)          | 36(56%)/ 26(44%)         | 69(60%)/ 47(40%) |
| Mean age            | 32.75±14.99 | 33.53±17.73              | 32.53±15.95              | 33.24±13.96  |
| Mean hospital stay  | 6.34±4.66 | 5.0±4.8                  | 5.5±4.5                  | 7.8±4.74     |

Footnotes: Males predominant, more younger age group and mean hospital stay was 6.34±4.66 days.

In our study, fever was present in all 200 (100%) patients. Vomittings, body pains, shortness of breath, headache, pain abdomen, rash, loose stools, arthralgia, jaundice, retro-orbital pain and low back pain, generalized weakness was complained by 82 (41%), 76 (38%), 46 (23%), 44 (22%), 42 (21%), 40 (20%), 22 (11%), 10 (5%), 10 (5%), 8 (4%), 4 (2%), and 1 (0.5%) patients respectively(Table 2).

Table 2: Various symptoms complained by Patients with Dengue infection

| Symptoms               | No. Of Patients (%) |
|------------------------|---------------------|
|                        | Total (n=200)       |
|                        | DF without warning signs (n=22) |
|                        | Dengue with Warning signs (n=62) |
|                        | Severe Dengue (n=116) |
| 1. Fever               | 200(100%)           |
| 2. Vomittings          | 82(41%)             |
| 3. Body pains          | 76(38%)             |
| 4. Shortness of breath | 46(23%)             |
| 5. Headache            | 44(22%)             |
| 6. Pain abdomen        | 42(21%)             |
| 7. Rash                | 40(20%)             |
| 8. Loose Stools        | 22(11%)             |
| 9. Back Pain           | 4(2%)               |
| 10. Arthralgias        | 10(5%)              |
| 11. Jaundice           | 10(5%)              |
| 12. Retro orbital Pain  | 8(4%)               |

Footnotes: Fever was the universal symptom.

In this study clinical signs were as following: Rash was seen in 100 (50%), pallor 80 (40%), bleeding manifestations 78 (38%), hepatomegaly 30 (15%), splenomegaly 28 (15%), conjunctival congestion 18(9%). Among bleeding manifestations, malena was seen in 44 (22%), hematuria 10 (5%), gum bleeding 8 (4%), hematemesis 4 (2%), epistaxis 4 (2%), menorrhagia 4 (2%), hemoptysis 2 (1%) and intracranial bleed in 2 (1%). (Table 3&4).
In our study population mean hemoglobin in males and females was 13.5±2.6 and 11.6±2.6gm/dl respectively. Mean PCV was observed as 34.7±8.1, 40.7±8.1 in males and females respectively. Mean Total Leukocyte Count (TLC) was 73±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was observed in 3% of patients. Atypical and transformed lymphocytosis were found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm. Leukopenia, leukocytosis, relative lymphocytosis was found in 64(32%), 30(15%), and 6915±5233 cells/cu.mm.

In our study, a total of 200 patients were included and the ratio of male to female was 1:4.1 which is consistent with the other Indian studies [6]. Age-wise distribution showed predominantly younger age group involvement. The frequency of patients below 40 yrsis 73%. This finding is consistent with other studies [6]. Statistical analysis showed no significant difference found in the mean age of the three grades. The increased daytime activity of the younger age group could be the reason for more exposure and more disease incidence. Analysis of symptomatology concluded fever is a universal complaint followed by vomitings, body pains, headache, pain abdomen, and shortness of breath. The typical symptoms of headache and retro-orbital pain were seen in 26% when compared to 20% in a study by Seet RC [7]. Pain abdomen and vomitings may be confused with febrile illness with gastrointestinal involvement such as typhoid, scrub typhus leptospirosis, and enteroviral gastroenteritis. WHO revised the Dengue classification criteria [5] in 2009 as undifferentiated fever, Dengue Fever without Warning Signs, Dengue Fever with Warning Signs, and Severe Dengue. In our study, we adhered to this new classification system. In our study, a total of 200 patients were included and the ratio of male to female was 1:4.1 which is consistent with the other Indian studies [6].

### Table 4: Different bleeding manifestations in Patients with Dengue Infection.

| Bleeding manifestations | No. Of Patients (%) |
|-------------------------|---------------------|
|                         | Total (n-200)       | Dengue without warning signs (n-15) | Dengue with warning signs (n-45) | Severe dengue (n-88) |
| 1. Malena.              | 44(22%)             | 0                                  | 16(35%)                         | 28(31%)               |
| 2. Epistaxis.           | 4(2%)               | 0                                  | 0                               | 4(4%)                 |
| 3. Gum bleeding.        | 8(4%)               | 0                                  | 0                               | 8(9%)                 |
| 4. Hematuria.           | 10(5%)              | 0                                  | 0                               | 10(11%)               |
| 5. Hemoptysis.          | 2(1%)               | 0                                  | 0                               | 2(2%)                 |
| 6. Hematemesis.         | 4(2%)               | 0                                  | 1(2%)                          | 3(3%)                 |
| 7. Menorrhagia.         | 4(2%)               | 0                                  | 1(2%)                          | 3(3%)                 |
| 8. Intracranial bleed.  | 2(1%)               | 0                                  | 0                               | 2(2%)                 |

**Footnotes:** Malena is the most common bleeding manifestation.

### Discussion

Elucidation of the clinical profile in dengue fever is important for understanding the disease and patient management. The clinical manifestations of Dengue are varied and confuse the physician with other endemic diseases which were prevalent in this area, such as typhoid, leptospirosis, scrub typhus, and Enteroviral gastroenteritis. Who revised the Dengue classification criteria [5] in 2009 as undifferentiated fever, Dengue Fever without Warning Signs, Dengue Fever with Warning Signs, and Severe Dengue. In our study, we adhered to this new classification system. In our study, a total of 200 patients were included and the ratio of male to female was 1:4.1 which is consistent with the other Indian studies [6].

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Loose stools were seen in 22(11%) patients. Vejchapipat P et al found frequent involvement of intestinal mucosal injury in dengue with utilizing I-FABP as a marker of injury [10]. In our study bleeding manifestations were seen in 82(41%) patients, a finding consistent with the study by Rachel et al. [6], whereas higher proportions of bleeding manifestations were noted by Sharma et al. [8] and Horvath [11] from Australia. Malena was seen in 44(22%) patients followed by hematuria (5%), gum bleeding (4%) hematemesis (3%), and...
epistaxis (2%). The above findings are similar to a study by Ratageri et al. in which GI bleeds were seen in 22% and petechiae in 18%.

The gastrointestinal tract was the predominant site of bleeding observed in the present study in comparison to other series reported by Sharma et al, from India. Rare bleeding manifestations such as intracranial bleeding were seen in 2 patients. One patient had a subdural hematoma, and the other with intraparenchymal bleed.

Hematura as a bleeding manifestation was seen in 7(3.5%) patients, where all were associated with severe dengue. Hemoptysis is seen in 3(1.5%) patients of the study population and all were associated with severe dengue.

Leucopenia was found in 32% of the study population. Most often it was blanching erythematous described as “white islands in a sea of red” followed by the petechial type, further, the rash was found on clinical examination in 100 (50%) patients. Cutaneous involvement was seen in 46.8% of patients in a North Indian study done by Thomas EA et al. The characteristic exanthem of DF is estimated to occur in 50-82% of patients with DF but few had petechial rash also.[14]

Conjunctival congestion was seen in 18 (9%) patients. This finding was found almost equally in all grades. Clinically significant pallor was noticed in 37(18%) patients of the study population.

Hepatomegaly was found in 30 (15%) patients of the study population. Hepatomegaly is one of the common findings of dengue infection. Rajoo Singh et al found a similar number (14.5%) of hepatomegaly in his study.[15] Splenomegaly was seen in 28 (14%) patients of the study group.

Leucopenia was found in 32% of the study population in contrast to a study by Gener d et al found an incidence of 62%. This higher incidence can be explained by the differences in the cutoff values. (in General et al study ≤5000 was considered as leucopenia, whereas in our study it was ≤4000).

Leucocytosis and relative lymphocytosis were found in 15% and 2.5% respectively in the study group and most of the cases are associated with severe dengue. The mean leucocyte count was comparatively high in severe Dengue patients.

Thrombocytopenia and haemoconcentration (rising hematocrit from baseline of 20% or more) representing the pathophysiological hallmarks of abnormal hemostasis and plasma leakage, respectively are constant laboratory findings. These changes occur simultaneously before the subsidence of fever and onset of shock. Therefore, they are important for clinical diagnosis.[13] Thrombocytopenia at admission was found in 71% of the patients and most of them had mild to moderate grade (30000-100000). Platelet dysfunction may be both quantitative or qualitative. Proposed mechanisms include bone marrow hypo-cellularity, immune-mediated destruction, and exhaustion triggered by immune complexes.[18]

Deranged liver function is common in patients with dengue infection due to direct attack on liver cells or unregulated host immune response against the virus.[15]. The degree of liver dysfunction in dengue infection varies from mild injury with the elevation of aminotransferases alone to severe injury with jaundice and even fulminating hepatic failure.[19]. In our study mild to moderate hepatitis was found in 80% and severe disease in 10% of patients which is consistent with Wong et al.[20]. The mean value of elevated SGOT (143.4) was greater than that of SGPT (120.9) for mild to moderate hepatitis.

Whereas the mean values for SGPT (1613.4) were higher than that of SGOT (1367.4) in severe dengue. Elevated Alkaline Phosphatase (ALP) was found in a significant proportion (35%) of patients, in this study. Similar figures for elevated ALP were found in 32% of the Dengue infections by Rajoo Singh et al.[15]. Elevated bilirubin was found in 14% of the study population. Other studies have shown jaundice in 3%-19%.[15]. There was no statistical significance in mean bilirubin values between different grades of dengue in our study.

Shah has reported high mortality in dengue patients with hepatitis.[21] In our study, no statistical significance in mortality was found in severe hepatitis. Hypoalbuminemia was found in 42% of the study population and its prevalence was more in severe dengue. Similar findings were found in other studies.[22]. Mean albumin levels correlated with mortality and risk of severe bleeding.

Most studies on the mechanisms of bleeding in DHF identified consumptive coagulopathy in a large proportion of cases. All severe cases with shock have coagulopathy, manifested by a prolonged partial thromboplastin (aPTT) time.[23, 24]. Elevated aPTT was seen in 40% of the study patients, most of the cases were associated with severe Dengue (48%). Renal failure was found in 4.5% of the study population. Glomerular injury secondary to immune complex deposition from dengue antigens is recognized as the etiology of renal injury. Mild mesangial proliferation, deposition of IgG, IgM, and C3, and thickening of the glomerular basement membrane with dense spherical particle deposition were demonstrated in DHF patients.[25]. Albuminuria was found in 25% of the study group, the higher prevalence was noted in patients with severe Dengue group, a finding consistent with a study by Adisorn et al.[26]. Hematuria was found in 33% of the population. Patients with severe Dengue grades had a higher prevalence of hematura when compared to other grades but not statistically significant. Adisorn et al.[26], (30.3%) found similar figures in their study group.[24]. Renal injury manifesting as raise in serum creatinine, proteinuria, glomerulonephritis, and acute kidney injury has been reported in dengue patients.[27]. In our study, all patients with renal failure were associated with severe Dengue grade, and most of the patients presented with hypotension. Lee et al. and Abboud[28] reported 4.5% and 5% of AKI in their study groups, the findings were similar to our studies.

Chest roentgenographic abnormalities were found in 28% of the study cohort. Most of the radiographs had effusions alone (20%) compared to the other abnormalities such as infiltrates (5%) and ARDS (3%). A study done by Chin Chou et al.[29] found a higher proportion (53%) of radiographic abnormalities. Wang et al reported an incidence of 1.8%of ARDS in their study involving 606 dengue patients in china.[31].

Ultrasound abdomen can be useful for the early recognition of ascites. 18% of total and 25% of severe dengue patients had ascites in our study.

Gall bladder wall thickness more than 5 mm can be adopted as a criterion for identifying DF patients at high risk for developing hypovolemic shock in dengue infection with a specificity of 92%.[32]. In our study 24(12%) patients had gall bladder wall edema.[33]. Acalculous cholecystitis was found in 12% of the study population of which most cases were associated with
Severe Dengue grade. Arboviral infection that can cause myocardial damage, either by direct infection or an autoimmune reaction, can lead to myocarditis. The presence of bradycardia and elevated cardiac enzyme levels (LDH and CPK) and 2D ECHO findings were consistent with a diagnosis of myocarditis. It can manifest as complete AV block or ventricular arrhythmias leading to syncope or palpitations [34-35]. Cardiac rhythm disturbances, such as bradycardia and ventricular ectopic, are known to occur during the convalescence period [36]. ECG changes in Dengue Fever include sinus bradycardia, ST-segment elevation, and non-specific ST-T changes [37]. Most of these changes were transient and revert to normal at follow-up. In our study bradycardia was seen in 15% and myocarditis in 3%. Lateef et al found similar findings in their cohort [38]. Systemic complications were observed in 50% of our study population. All were associated with severe Dengue. Severe bleeding was seen in 24%, whereas Lum et al found a similar observation in 20% of patients [39]. Predictors of severe bleeding with statistical significance were: Mean platelet count at admission, Serum albumin, and prolonged aPTT. There have been reports of neuromuscular complications of dengue virus infection and include encephalitis, myelitis, Guillain Barre (GB) syndrome, and myositis [40]. In our study Neurological complications were seen in 6% of patients. Multi-system involvement was seen in a significant proportion of patients. Approximately one-fourth of the entire population developed multisystem involvement. The higher proportion of multisystem involvement may be due to referral bias as our hospital is a tertiary care hospital. Studies were showing multisystem involvement up to 50% where most of the cases were admitted in ICU [41]. Predictors of severe bleeding were: Mean platelet count at admission, Serum albumin, and Prolonged aPTT. (Table 5)

Table 5: Correlation of clinical variables in patients with or without Severe bleeding.

| Clinical variables | Absent (n=152) | Present (n=48) | P-value |
|--------------------|---------------|---------------|---------|
| Age in years       | 33.58±15.59   | 31.06±11.83   | 0.404   |
| Male               | 83(54.6%)     | 32(66.6%)     | 0.192   |
| Female             | 69(43%)       | 16(33.3%)     |         |
| Duration of fever  | 6.02±3        | 5.77±2.69     | 0.683   |
| Hemoglobin         | 12.87±2.47    | 12.61±3.22    | 0.626   |
| TLC                | 6827.52±5172.27 | 7245.16±5534.49 | 0.694   |
| Platelet count at admission | 80743.59±60150.12 | 42935.48±43044.11 | 0.001** |
| Platelet count at discharge | 119401.7±61522.22 | 95322.58±99456.32 | 0.095 |
| Lowest platelet count | 62196.58±48494.56 | 31483.87±25837.79 | <0.001** |
| SGOT#              | 275.21±52.95  | 395.42±101.55 | 0.299   |
| SGPT#              | 202.8±61.18   | 194.32±49.39  | 0.945   |
| Albumin            | 3.04±1.46     | 2.85±6.64     | 0.007** |
| APTT               | 36.9±13.36    | 45.48±21.02   | 0.006** |
| NS1 positivity     | 80(52%)       | 42(88%)       | 0.189   |
| Ig M               | 1.64±0.88     | 1.7±1.04      | 0.761   |
| Ig G               | 1.85±1.37     | 1.86±1.59     | 0.984   |
| Mortality          | 6(83.3%)      | 5(83.3%)      | 0.167   |

Footnotes: Predictors of severe bleeding were: Mean platelet count at admission, Serum albumin, and Prolonged aPTT.

97% of dengue patients were discharged in stable condition. Mortality was noted in 3% of the study population and all had severe Dengue. This mortality rate was consistent with the other studies [6]. Female sex, mean hemoglobin, mean TLC, and mean albumin were the statistically significant variables associated with mortality. (Table 6)

Table 6: Comparison of clinical variables of expired and discharged patients with Dengue.

| Clinical variables | Outcome | Expired (n = 6) | Discharged (n = 194) | P-value |
|--------------------|---------|---------------|----------------------|---------|
| Age in years       | 32.75±14.69 | 41.8±19.4 | 0.182   |
| Male               | 115(59%)      | 1(16%)       | 0.013*   |
| Female             | 79(40.7%)     | 5(83.3%)     |         |
| Duration of fever  | 5.92±2.89      | 7.2±4.49     | 0.340   |
| Hemoglobin         | 12.9±2.6      | 10.3±2.6     | 0.029*   |
| TLC                | 6666.57±5051.35 | 14020±5957.1 | 0.002** |
| Platelet count at admission | 73902.1±59496.75 | 42000±26124.7 | 0.235 |
| Platelet count at discharge | 115454.55±17991.07 | 83000±47381.43 | 0.320 |
| Lowest platelet count | 56489.51±43783.54 | 35000±25000 | 0.278 |
| SGOT#              | 303.47±48.56  | 212.2±61.14  | 0.772   |
| SGPT#              | 203.15±51.11  | 140.2±34.09  | 0.819   |
| Albumin            | 3.18±2.08     | 2.42±14      | <0.02*   |
| APTT               | 38.47±14.49   | 45.4±37.8    | 0.330   |
| NS1 positivity     | 116(60%)      | 6(100%)      | 0.180   |
| Ig M               | 1.67±0.93     | 1.12±0.36    | 0.188   |
| Ig G               | 1.83±1.34     | 2.56±3.03    | 0.268   |

Footnotes: predictors of mortality were: Female sex, Mean hemoglobin, Mean TLC, and Mean albumin.

Limitations of the study include the small size of participants, single institutional study, non-inclusion of specific
inflammatory biomarkers like IL 6 which play a major role in pathogenesis, lack of serotyping data of DENV.

Conclusions

- Fever was a universal symptom followed by vomitings, myalgias, headache, and rash.
- The rash was the most common physical finding which is blanching in nature.
- Malena was the most common form of bleeding manifestation.
- Predictors of severe bleeding include, mean platelet count at admission, serum albumin, and prolonged aPTT.
- Predictors of mortality include female sex, mean hemoglobin, Mean TLC, and mean albumin.

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