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*RESEARCH ARTICLE*

# PREDICTORS OF SEVERITY OF DENGUE IN PATIENTS ADMITTED TO ICU: A CROSS SECTIONAL STUDY

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## *Abstract*

**Background & Objectives:** Dengue mostly causes a mild self-limiting disease but a small proportion may progress to develop severe dengue clinical manifestations, which require interventions in intensive care. The objective of the study was to describe the clinical profile, course, and outcome of dengue-infected patients admitted to intensive care units (ICU) and to evaluate factors associated with morbidity and mortality.

**Methods:** This is an observational, descriptive study. Patients above the age of 18 admitted directly or transferred to ICU from another ward with serological evidence of dengue (positive NS1 antigen and/or IgM antibodies to dengue) were included in the study. The severity of the illness was assessed using APACHE and SOFA Scores. The primary outcome was mortality, while the secondary outcome was the length of stay in the ICU.

**Results:** A total of 80 patients were studied and the mean age of the study subjects was 36.53 (± 15.28) years. The median duration of ICU stay was 2 days with an IQR of (1-3) days. The mean APACHE was 21.53 (±10.91) while the mean SOFA score was 12.05 (± 4.70). The area under the curve for the WHO classification of severe dengue was 79%, with a positive predictive value of 58.70. The area under the curve for lactate was 89% with a positive predictive value of 90.48.

**Interpretation & Conclusion:** Lactate alone is a good predictor of mortality in severe dengue. APACHE and SOFA scores are good predictors of mortality.



## Introduction:-

Dengue is an arthropod-borne viral disease with increasing prevalence in the last three decades. It is a major public health concern throughout the tropical and subtropical regions of the world. One modeling estimate indicates 390 million dengue virus infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) [(1)]. Another study on the prevalence of dengue estimates that 3.9 billion people are at risk of infection with dengue viruses. Despite a risk of infection existing in 129 countries [(2)], 70% of the actual burden is in Asia [(1)]. The number of dengue cases reported to WHO increased over 8 fold over the last two decades, from 505,430 cases in 2000 to over 2.4 million in 2010, and 5.2 million in 2019. Reported deaths between the years 2000 and 2015 increased from 960 to 4032, affecting mostly the younger age group.

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In today's public health scenario, the significance dengue holds cannot be overstressed. Dengue infection can result in severe clinical manifestations requiring intensive care[3]. In this context, it becomes imperative that the primary care physician be aware of the varied presentations of this disease. This will lead to early recognition of the complications so that by effective triage the morbidity & mortality due to the disease can be brought down. However, there is limited knowledge on early risk factors of intensive care unit (ICU) requirements.

The objective of the study was to describe the clinical profile, course, and outcome of dengue-infected patients admitted to intensive care units (ICU). The study also evaluated factors associated with mortality and morbidity.

## Methodology:-

It was a cross-sectional study done by the Department of General Medicine in collaboration with the Intensive Care Department of St. John's Hospital. All patients were admitted with Dengue to the ICU from 2015 November to January 2017. Diagnosed cases of Dengue who fit the criteria were included in the study. Using WHO 2009 classification and case definition patients were classified into Dengue without warning signs, Dengue with warning signs, and Severe Dengue. Patient demographics, clinical presentation & laboratory parameters were collected in detail using the predesigned proforma. The severity of illness was assessed based on ICU severity scores APACHE and organ failure based on Sequential Organ Failure Assessment (SOFA). After obtaining consent from the subject or from a first-degree relative, details were collected as per a pre-set questionnaire.

Institutional Ethics Committee (IEC), St. John's Medical College, Bangalore approved the conduct of the study. IEC Study Ref No: 295/2015.

**Sample size calculation**

Based on a search of the literature, a study conducted by Sidharth et al. [4], reported ICU mortality of Dengue patients as 10%. Considering an estimated proportion of 0.10, an alpha error of 5%, and a confidence interval of 90%, the sample size obtained was 100 patients. We have taken a convenient sample of 80 patients to conduct this study at our hospital.

**Analysis**

Data were analyzed using STATAver 12. Bivariate analysis was done with the primary outcome as a dependent variable versus independent variables. T-tests were used for continuous variables and Chi-Square/Fisher's test was used for categorical variables. The variables that were identified as significant in the bivariate analysis were put into a logistic regression model with the primary outcome as the dependent variable. The area under the curve (AUC) for the WHO clinical classification, APACHE, SOFA scores, and lactate as predictors of mortality were calculated along with their sensitivity, specificity, and positive predictive value. For all statistical testing, $p < 0.05$ was considered significant.

## Results:-

Eighty patients who were serologically dengue positive (NS1 and IgM) and admitted to the ICU were observed in this study. The primary indications for ICU admission were hypovolemic shock in 24 (30%) subjects, respiratory distress in 24 (30%) subjects, and both (shock + respiratory distress) in 32 subjects (40%). Out of the 80 patients, 52 (65%) survived the ICU, while 28 (35%) died in the ICU with the mortality in those above 70 years being 100%. The mean Age of the study subjects was 36.53(±15.28). The median duration of stay in the ICU was 2 days (IQR 1-3). The demographic details, clinical characteristics, and laboratory parameters are described in Tables 1 and 2.

**Table 1:-** Bivariate analysis between survivors and non-survivors (demographic and clinical characteristics):

| Baseline Parameters | Survivors (N = 52) | Non Survivors (N=28) | P value |
|---|---|---|---|
| Age Mean(SD) | 33.13 (±13.15) | 42.85 (±17.10) | 0.0120 (t test) |
| Sex(M, F)(N) | 26,26 | 16,12 | 0.639 (Chi Sq test) |
| APACHE Mean (SD) | 14.71 (±5.43) | 34.21 (±6) | 0.00 (t test) |
| SOFA Mean(SD) | 9.26(±2.63) | 17.21(±2.99) | 0.00 (t test) |
| Duration of stay in ICU Median (IQR) | 2(1,3) | 2(1,4) | 0.031 (Fisher'stest) |
| WH O ( severe | 19 | 27 | 0.00 (Chi Sq test) |

| | | | |
|---|---|---|---|
| Dengue) | | | |
| Cardiac(N) | 6 | 6 | 0.252(Chi Sq test) |
| Diabetes(N) | 5 | 5 | 0.303 (Chi Sq test) |
| Thyroid(N) | 2 | 2 | 0.519 (Chi Sq test) |
| Pregnant | 2 | 2 | Aa |

**Table 2:-** Bivariate analysis between survivors and non-survivors based on Laboratory parameters.

| Laboratory Parameters | Survivors (N = 52) | Non Survivors (N=28) | Pvalue |
|---|---|---|---|
| NS1 (N) | 32 (51.5%) | 15 (53.5%) | 0.537(Chi Sq test) |
| IGM (N) | 37 (71.1%) | 18 (64.2%) | 0.527(Chi Sq test) |
| Lowest Platelet count(Mean, SD) | 39394 (±31697) | 34535 (±27544) | 0.4784 (t test) |
| APTT(Mean, SD) | 45.14 (±16.3) | 47.45(±26.49) | 0.6811(t test) |
| AST(Median) | 258 | 529.5 | 0.482 |
| ALT(Median) | 123.5 | 196 | 0.48 |
| PCV(Mean, SD) | 35.73 (±8.88) | 34.93 (±8.58) | 0.6958(t test) |
| Leucocyte(Mean, SD) | 9051 (±6484) | 13128 (±10764) | 0.0747(t test) |
| Lactate(Mean, SD) | 4.07 (±2.1) | 10.03 (±4.21) | 0.000(t test) |
| PH(Mean, SD) | 7.32 (± 0.1) | 6.98 (±0.13) | 0.000(t test) |

The primary indications for ICU admission were hypovolemic shock in 24 (30%) subjects, respiratory distress in 24 (30%) subjects, and both (shock + respiratory distress) in 32 subjects (40

There was no significant difference in the proportions that received platelet transfusions between the non-survivors and survivors. A significantly greater number of non-survivors required mechanical ventilation, renal replacement therapy, and vasopressors than the survivors ($p<0.05$). The complications seen among survivors and non-survivors are depicted in table 3.

**Table 3:-** Bivariate analysis between survivors and non-survivors based on complications.

| | Survivors | Non Survivors | Pvalue |
|---|---|---|---|
| ARDS(N) | 5 (9.61%) | 16 (57.14%) | 0.000 (Chi Sq test) |
| | 24 (46.15%) | 16 (57.14%) | |
| | Mean AST | Mean AST | |
| Hepatitis(N) | 1255.92 (±2727.78) IU/L | 1820.18(±3189.30) IU/L | 0.482 ( t test) |
| Encephalopathy(N) | 4 (7.69%) | 3 (10.71%) | 0.648 (Chi Sq test) |
| Renal Failure(N) | 9 (17.30%) | 22 (78.57%) | <0.001 Chi Sq test |
| Shock(N) | 36 (69.23%) Mean MAP: 64.59 (±16.14)mmhg | 26 (92.85%) Mean MAP: 51.42 (±12.87)mmhg | 0.002 ( t test) |
| Myocarditis(N) | 30 (57.69%) | 23 (82.14%) | 0.027 Chi Sq test |
| Polyserositis(N) | 32(61.53%) | 21(75%) | 0.225 (Chi Sq test) |

Out of the four pregnant women who were admitted to the ICU with dengue, two died, one developed multiorgan failure post lower segment cesarean section while the other died due to hypovolemic shock.

## Discussion:-

The mean age of the patients in this study was 36.53 (±15.28) years. It was observed that the mean age of dengue patients in the ICU reported by Juneja et al was 39.6 (± 17.1) years[(5)]Most studies conducted in ICU had a younger subject, including our study reflecting the younger age group that dengue generally affects.

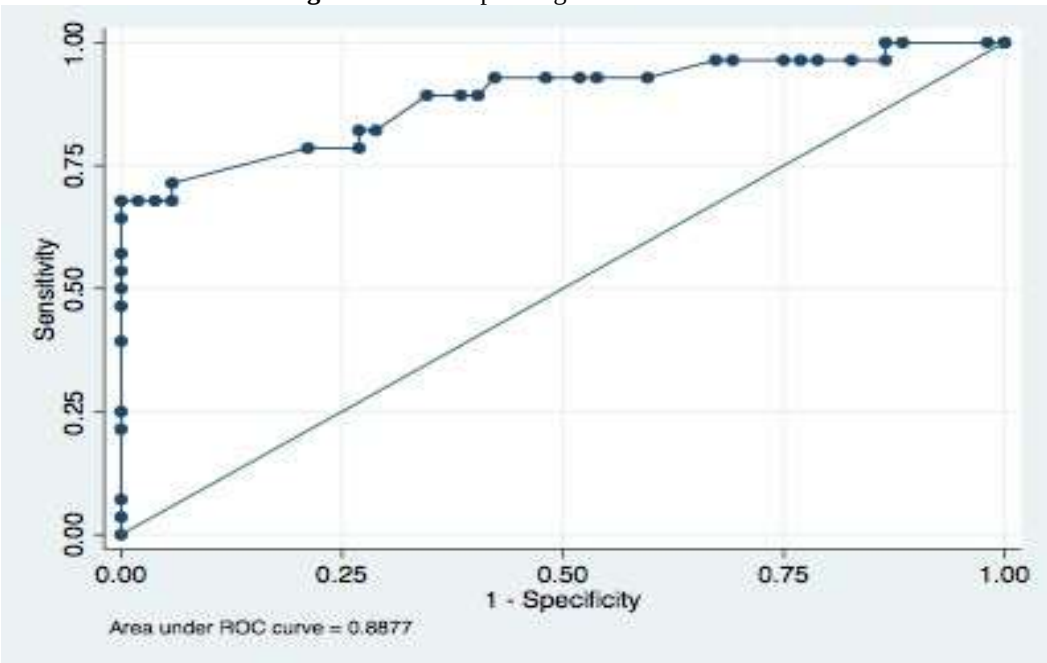
The in-ICU mortality rates observed in our study were higher compared to similar Indian studies. The present study had an in-ICU mortality rate of 35% (28 patients). Other Indian studies have reported variable ICU mortality rates ranging from 6%-10%. Whereas a study from Brazil by Amancio et al[6] reported in-ICU mortality of 38% (37 patients) which was similar to our study. This was probably because 62 (77%) of patients in our study were in shock while 44(55%) had severe lactic acidosis. Studies have shown mortality rates to be higher in patients with shock [5,7,8,9,10].

Severity scales are important adjuncts of treatment in the intensive care unit (ICU) in order to predict patient outcomes, comparing the quality of care and stratification for clinical trials. Even though disease severity scores are not the key elements of treatment, they are, however, an essential part of improvement, in clinical decision-making and in identifying patients with unexpected outcomes.

This study included the APACHE II score to predict ICU mortality and the SOFA score to assess the severity of multiple organ failure. The mean value of the APACHE II score and SOFA score in the Non-Survivors was 34.21(±6) and 17.21(±2.99) respectively. The studies conducted by Juneja et al[5] and Siddharth et al[4] also used the severity scores APACHE and SOFA scores. Juneja et al[5] observed the mean value of the APACHE II score and SOFA score in the non-survivors was 30.25 (± 5.8) and 13.42 (± 3.1 ). In Siddharth et al[4] study, observed the mean value of the APACHE II score and SOFA score in the non-survivors was 25.45 (±8.5) and 14.24 (±1.3) respectively. Based on the ICU severity scores our study showed that the subjects were sicker compared to Juneja et al[5] and Siddharth et al [4] and so too the mortality was higher compared in both the studies.

The study done by Thanachartwet V et al[11] showed that patients having lactate levels ≥2.0 mmol/L found were associated with the development of severe dengue. Elevated lactate levels were observed to correspond with the severity of dengue in our study. Yacoub S, et al. (2017) [12] study showed lactates in dengue patients on the first day of admission to ICU are associated with severe outcomes of recurrent shock and respiratory distress. Sirikit P et al[13]found elevated lactate levels in DHF and/or DSS patients. They concluded that lactate could be a predictor of DSS if the level is > 2U/L on Day Zero. In our study too there was a strong association between lactates and survival and proved that it could be used as a predictor of mortality. Lactate was found to have a sensitivity of (67.86%) and specificity (96.15%) with a cut-off value of 6.8. The higher lactate level in patients with severe dengue is due to severe volume depletion from plasma leakage causing tissue hypoperfusion, hypoxia, and anaerobic glycolysis. Another mechanism for hyperlactatemia is reduced hepatic clearance and the liver itself can produce lactate due to hepatic ischaemia[14].

**Fig 1:-** Receiver operating curve for Lactate.



Sensitivity 67.86%
Specificity 96.15%
Positive predictive value 90.48%

The limitations of the study were the patients were not followed up in the ward and also after discharge. The study was of short duration and it covered only one epidemic. It would have been ideal to calculate hospital length of stay and mortality 28 day and 90 day mortality.

## Conclusion:-

Lactate showed a strong association with survival and predicted mortality. Hence, lactate alone can be used as a good discriminant for predicting mortality. The severity scores in ICU - APACHE II and SOFA predicted mortality and multi-organ failure. Laboratory tests such as platelet count, hematocrit, AST/ALT, APTT, and total WBC count are not necessarily good predictors of mortality.

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