Original Research Article

Sequential APACHE II Scores for Prediction of Mortality in Patients Admitted to Critical Care Areas With Severe Malaria

ABSTRACT

Background/Aims: Both generic and disease specific prognostic scoring systems have been employed in critical care areas. The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a generic point score which provides general assessment of illness and severity. This study seeks to determine the ideal time point for the APACHE II score in predicting the mortality of critically ill malaria patients.

Materials and Methods: This longitudinal study was conducted after getting necessary ethics committee approval. APACHE II scores on days 0, 2 and 7 were evaluated and appropriate statistical tests were applied.

Results: Out of 120 patients, there were 54 patients of P.vivax, 60 of P.falciparum and six patients with mixed infection. Mean APACHE II score was maximum on day 0 followed by day 2 and 7 in decreasing order. The APACHE II score was statistically greater on all days in patients who didn't survive. The Receiver Operating Characteristic (ROC) curve when plotted showed APACHE II score on day 2 with cut-off ≥14 to be the most valid in mortality prediction with a sensitivity of 64.28% and specificity of 87.80% as most of the results were on the left from the diagonal line and had greatest area under the curve.

Conclusion: APACHE II was found to be a useful prognostic score in severe falciparum/vivax malaria who needed intensive care treatment as sequential score gives significant difference in survivors and non-survivors on second day. Day-2 APACHE II score is an optimal biomarker to predict the outcomes of ICU patients; 14 is the best cut-off for defining patients at high risk of mortality.

Key words: Malaria, APACHE II, Vivax, Falciparum, Prognostic score.

Key message: Malaria is a major cause of tropical sepsis in India leading to significant amount of mortality. Sequential APACHE II scoring could have a role in evaluation of effectiveness of treatment, trend in recovery or dysfunction and prediction of mortality.

Keywords: Malaria, APACHE II, Vivax, Falciparum, Prognostic score..

INTRODUCTION:

The prognosis of a critically ill patient is evaluated in an ICU setting using a variety of grading techniques. APACHE score is one such generic, non-disease or organ-specific

scoring system, which was introduced in 1981. The APACHE score is computed using "one time" data within the first 24 hours of ICU admission in order to predict mortality [1]. A dynamic score has higher applicability in sepsis, tropical sepsis, and malaria for prognosis because it shows a trend in recovery or dysfunction [2]. With the hypothesis that patients who are critically ill from malaria (falciparum and vivax) could benefit from the same insight provided by sequential APACHE II, this study was undertaken. The study also seeks evaluate the role of this score in predicting ICU mortality.

MATERIALS AND METHODS: This was a longitudinal study, conducted at a rural teaching hospital located, in Vadodara, Gujarat. The study was conducted after obtaining approval from Institutional Ethics Committee (SVIEC/ON/MEDI/BNPG12/D123080). Patients who were admitted to ICU and critical ward fulfilling inclusion and exclusion criteria were studied.

Inclusion criteria:

- The present study included patients with severe malaria, defined as those having smear positive malaria with multi organ involvement who were admitted in ICU and emergency ward. Patients of both falciparum and vivax malaria were included.

Exclusion criteria:

- Patients in whom protocol of investigations/ assessment that was required for APACHE II scoring like Glasgow Coma Scale(GCS), urine output, serum creatinine, blood urea, serum bilirubin, blood glucose, haemoglobin, platelet count, and total leucocyte count, could not be recorded properly, such patients were excluded.
- Patients below age of 18 years were also excluded.

Between the research periods, a total of 120 willing patients who met the inclusion and exclusion criteria and were available were taken. Out of these, 30 patients were admitted to the emergency room and 90 patients to the intensive care unit. 54 individuals had vivax

malaria, 60 had falciparum malaria, and 6 had mixed malaria. Field and Giemsa stains were used to identify malaria in each subject. There were thick and thin smears used. The plus technique was used to count the parasites [14,15].

CBC, platelet count, malaria antigen test, whole blood clotting time, PT, APTT, arterial blood gas analysis, blood sugar, RFT, LFT, serum electrolytes, and chest radiographs were among the laboratory tests that were conducted on admission in accordance with procedure. GCS, urine output, heart rate, blood pressure, breathing rate, and general and systemic exams were all part of the daily evaluation process. Patients that survived were monitored until they were discharged by the hospital.

On the day of admission, day two, and day seven, the score was calculated. Patients were divided in two groups namely "survivors" and "non-survivors", the scores were analysed between the two groups. A ROC curve was created (of 0, 2 and 7th day) using the worst APACHE II score for each of the 3 days. By employing a pivot table in an Excel sheet, specificity was plotted on the X axis from 0 to 1 and sensitivity was similarly plotted on the Y axis.

STATISTICAL ANALYSIS: Data from patient source files were imported into Excel and MS Office 13 and aggregated. Mean ± standard deviation and proportions where appropriate were calculated. Appropriate statistical tests were used: t-test for two population proportions and chi-square test for categorical values. The value of P OF etlt was considered; 0.05 task. ROC curves were plotted by calculating sensitivity and specificity 1, ie. False positive rate using the worst APACHE II data for the first seven days and deaths using a pivot table in an Excel worksheet. The area under the receiver operating curve (AUROC) was calculated.

RESULTS Out of 120 patients, 86 were males and 34 females. Two groups were formed, 82 patients who survived formed the ‘survivors’ group and 38 patients that died formed the ‘non-survivors’ group. There were 60 males and 22 females in first group while the latter had

26 males and 12 females. Mean age of survivors was 38.56±2.27 and that of non-survivors was 40.21±5.6 years (p=0.718). Out of 54 patients with P.vivax infection, 60 with P. falciparum infection and 6 with mixed infection, mortality was in 18, 15 and 05 patients respectively. On admission, 20 (16.67%) patients had 1+, 40 (33.33%) had 2+, 48 (40%) had 3+ and 12 (10%) had 4+ parasite count. There were 56 patients in survivor group and 4 in non-survivor group who had 1 to 2 plus parasite count while 26 in survivors group and 34 in non-survivor group had 3 to 4 plus parasite count. There was statistically significant higher parasite count (of 3+ and 4+) in patients who died than that of survivors (p-value=0 .0031). Mean APACHE II of all the three days were calculated. On day 0 and 2, Mean APACHE II was 18.9474 and 17.8947 in non-survivor group while it was 11.0488 and 10.2927, respectively in survivors group. Mean APACHE II on day 7 was 16.1579 in non-survivor group while 8.7073 in survivor group. As shown here, there was a decreasing trend of mean APACHE II in both groups over the course of disease. APACHE II was higher in non-survivors than in survivors.

ROC curve of APACHE II score on Day 0 (Fig: 1) shows that threshold on the curve that is close to the top left of the plot corresponds to APACHE II score of 19. Hence, greater discriminant capacity was observed at APACHE II score of ≥19. Mean APACHE II in non-survivor group was 18.94 and survivor group was 11.0488. Thus APACHE II score of day 0 gave prediction reaching cut-off value of ≥19. AUROC was 0.8426±0.0596 with 95% confidence interval (0.7234-0.9618) (p-value =0.013).

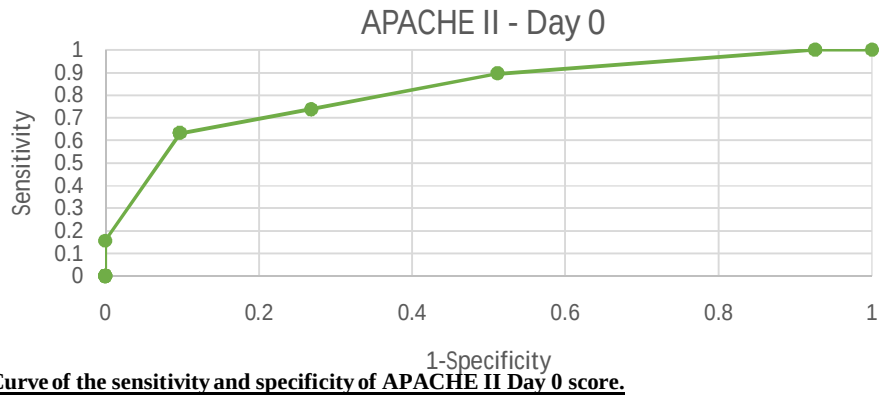

Fig1: Curve of the sensitivity and specificity of APACHE II Day 0 score.
In a Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (specificity) for the different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair that corresponds to a particular decision threshold. A test with perfect discrimination (no overlap between the two distributions) has a ROC curve that passes through the upper left corner (100‰ sensitivity and 100‰ specificity) here APACHE II score of ≥19. Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test. This ROC curve has an area of 0.8426±0.0596 with 95% confidence interval (0.7234-0.9618) (p-value =0.013)

ROC curve of APACHE II score on Day 2 (Fig: 2) shows that threshold on the curve that is close to the top left of the plot corresponds to APACHE II score of 14. Hence, greater discriminant capacity was observed at APACHE II score of ≥14. Mean APACHE II in non-survivor group was 17.8947 and survivor group was 10.2927. Thus APACHE II score of day 2 gave prediction reaching cut-off value of ≥14. AUROC was 0.8490±0.0481 with 95% confidence interval (0.7528-0.9452) (p-value =0.019).

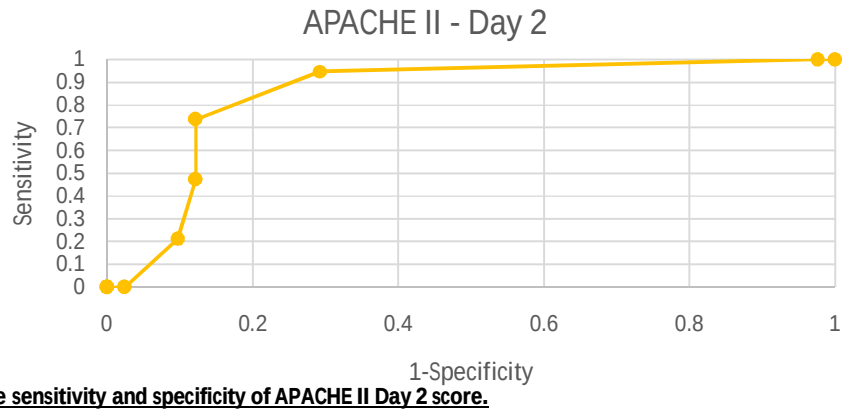

Fig2:Curve of the sensitivity and specificity of APACHE II Day 2 score.
In a Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (specificity) for the different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair that corresponds to a particular decision threshold. A test with perfect discrimination (no overlap between the two distributions) has a ROC curve that passes through the upper left corner (100‰ sensitivity and 100‰ specificity) here APACHE II score of ≥14. Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test. This ROC curve has an area of 0.8490±0.0481 with 95% confidence interval (0.7528-0.9452) (p-value =0.019)

ROC curve of APACHE II score on Day 7 (Fig: 3) shows that threshold on the curve that is close to the top left of the plot corresponds to APACHE II score of 14. Hence, greater discriminant capacity was observed at APACHE II score of ≥14. Mean APACHE II in non-survivor group was 16.1579 and survivor group was 8.7073. Thus APACHE II score of day 7 gave prediction reaching cut-off value of ≥14. AUROC was 0.7831±0.0586 with 95% confidence interval (0.6659-0.9003) (p-value =0.013).

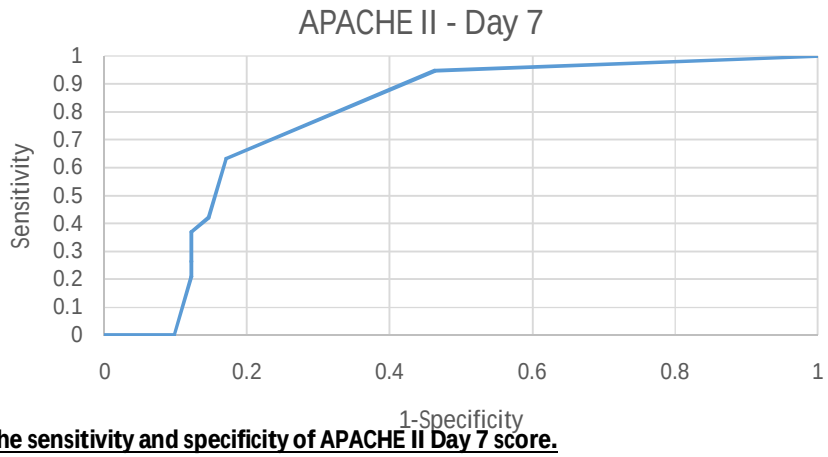

Fig3:Curve of the sensitivity and specificity of APACHE II Day 7 score.

In a Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (specificity) for the different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair that corresponds to a particular decision threshold. A test with perfect discrimination (no overlap between the two distributions) has a ROC curve that passes through the upper left corner (100‰ sensitivity and 100‰ specificity) here APACHE II score of ≥14. Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test. This ROC curve has an area of 0.7831±0.0586 with 95%

APACHE II score on day 2 had maximum sensitivity for prediction of mortality due to malaria and comparable specificity to day 0. AUROC of day 2 was greater compared to day 0 and 7. Thus we derived that APACHE II score calculated on day 2 had maximum predictive value for mortality due to malaria.

Table:1-Comparision of APACHE II scoring system on Days 0,2 and 7 for mortality prediction.

APACHE II Score	Sensitivity	Specificity	PPV	NPV	AUROC
Day 0	63.15%	90.24%	75.00%	84.09%	0.8426
Day 2	73.68%	87.80%	73.68%	87.80%	0.8490
Day 7	38.88%	80.64%	53.84%	69.44%	0.7831

PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUROC: Area Under the Receiver Operating Characteristic

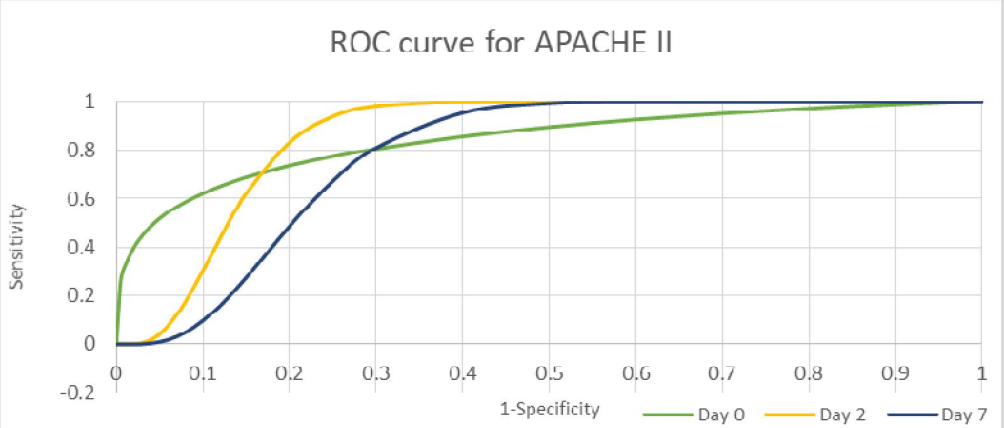

Fig4:Curve of the sensitivity and specificity of APACHE II Day 0 (Green), 2 (yellow) and 7 (Blue) score.

In a Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (specificity) for the different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair that corresponds to a particular decision threshold. A test with perfect discrimination (no overlap between the two distributions) has a ROC curve that passes through the upper left corner (100‰ sensitivity and 100‰ specificity). Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test. Here ROC curve for Day 1 has an area of 0.8426±0.0596 with 95% confidence interval (0.7234-0.9618) (p-value =0.013) , Day 2 has an area of 0.8490±0.0481 with 95% confidence interval (0.7528-0.9452) (p-value =0.019) and Day 7 has an area of 0.7831±0.0586 with 95% confidence interval (0.6659-0.9003) (p-value =0.013). Therefore APACHE II score calculated on Day 2 had maximum predicitive value for predicting mortality.

DISCUSSION –

Together with six other diseases (diarrhoea, HIV/AIDS, tuberculosis, measles, hepatitis B, and pneumonia), malaria causes a significant socioeconomic burden on humanity and accounts for 85% of the burden of infectious diseases worldwide [3, 4]. Ninety nations and territories in the tropics and subtropics are affected by malaria, with Africa south of the Sahara accounting for about half of them.

Around 2020 million people worldwide, or about 36% of the population, are at risk of acquiring malaria. According to the World Health Organization, there are 300–500 million cases of malaria each year, with 90% of those instances occurring in Africa. Additionally, > 75% of the estimated annual death from malaria in the world, which ranges from 700,000 to 2.7 million people, comes from children and expecting mothers from Africa. Because most hyper- and holoendemic nations, particularly in Africa, lack reliable diagnostic facilities and

reporting systems, concerns have been raised about the accuracy of these estimates [5, 6]. In the WHO's Southeastern Asia Region, 1.2 billion people—or 6% of the world's population—who reside in 11 countries and number 1.4 billion—are at risk of contracting malaria, with the majority of them residing in India [7]. But just 2.5 million of the world's malaria infections originated in Southeast Asia. India alone was responsible for 76% of all cases [6]. In 2018, the WHO reported that the majority of malaria deaths worldwide occurred in 20 countries in Sub-Saharan Africa and India, with 50% of those cases occurring in Nigeria, the Democratic Republic of the Congo, Mozambique, Uganda, and India, which together accounted for 25%, 11%, 5%, 4%, and 4% of all malaria cases globally, respectively [8]. Early detection of the risk factors may help in lowering the morbidity and mortality related to malaria as delayed diagnosis is one of the key variables associated with death [9]. Multi-organ failure can result from malaria, which is a kind of tropical sepsis [10,11]. The majority of falciparum malaria patients may exhibit severe symptoms and side effects, such as Multi Organ Dysfunction Syndrome (MODS) [12]. P.vivax malaria can result in deaths, multi-organ failure, thrombocytopenia, as well as severe and resistant malaria, like falciparum spp [13]. The prognosis of a patient is evaluated in an ICU setting using a variety of grading techniques. Acute Physiology and Chronic Health Evaluation (APACHE) score, Simplified Acute Physiology Score (SAPS), Sequential Organ Failure Assessment (SOFA) score, and others are a few of the techniques [12,13,14]. APACHE II is a severity of disease generic classification system. APACHE II calculates a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. Similar to our study Knaus WA et al found increasing score (range 0 to 71) was closely correlated with the subsequent risk of hospital death [11]. Aim of the present research was applicability of APACHE II scoring system in a rural population catering tertiary care teaching hospital. Malaria is a commonly encountered clinical problem for

which medical attention is needed. The present study was designed to find out applicability of sequential APACHE II scoring in patients who were admitted in critical care wards with vivax and/or falciparum malaria. Parasite count was a very important parameter in this study, patients having higher parasite density had increased risk of mortality. Admission parasite count of 3 to 4 plus was present in significantly higher number among non-survivors group than survivors. APACHE II score was significantly higher in non-survivors on all the days of admission. For initial risk assessment of mortality and morbidity/ MODS, parasitic count can also be a good prognostic marker while trend of APACHE II can predict mortality on further follow-up period. Ali H et al conducted a study in Karachi, it was found that high parasite density was associated with severe clinical illness, complications and mortality [15]. In this study, fatality rate was almost equal in both types; vivax and falciparum. Total 82 patients lived and 38 patients died. Amongst 54 patients suffering from P.vivax 36 patients survived and 18 patients died, while 45 patients survived and 15 died in group of falciparum malaria. Six patients had mixed infection, of which 5 died. In present study, mean APACHE II score on day 0, 2 and 7 was higher in non-survivors group when compared to survivors. Day 2 APACHE II score had maximum sensitivity and negative predictive value with comparable specificity to day 0 score. Thus day 2 APACHE II score with maximum AUROC and had maximum predictive value for in hospital mortality. If treatment with anti-malarial drugs and interventions for organ support was successful, decreasing/stationary trend was observed in scores. Thus, it can be implied that the scores increase when anti-malarial drugs fail to act optimally (drug resistance or presence of dysregulated host response to malaria). As per present study, serial scoring may show upward or downward trend, which is better prognosis indicator than a one-time severity assessment. In a similar type of study in patients of sepsis including that of malaria, serial measurement of SOFA score on third to seventh day (first week) was found to be a useful predictive tool than of day 0 (on admission) SOFA score and

APACHE-II score [11]. APACHE score is not disease specific and takes into account other host factors like “Age” and “Co-morbidities” while MSS is a disease specific score but does not take into account of “Age” and “Associated co-morbidities” like APACHE, while prognosticating risk of death due to malaria. In present study, age was not significantly different in survivor and non-survivor group. Sequential measurement of APACHE II can be recommended as compared to onetime score measurement. Parasite count can be added in prognosis scoring system as it is the specific indicator for malaria severity [16]. There is a still a need for novel, definite and specific, severity and prognostic scoring system model derived through prospective work which can efficiently predict the outcome of any patient suffering from severe malaria admitted to critical wards. Incorporating parasite count with severe organ dysfunction scoring system could increase the predictive values for these scoring system and remains a topic to be studied. Until a more accurate and validated specialised scoring system for sepsis is developed, the APACHE II score and other prognostic scoring models may continue to be useful tools for prediction and prognostication [17].

CONCLUSION(S): APACHE II scoring system was found to be useful prognostic score in severe falciparum/ vivax malaria who needs intensive care treatment as sequential score giving significant difference in survivors and non-survivors on all days while parasitic count on day of admission can good predictive tool for mortality on the day of admission. Day 2 APACHE II scores had overall better performance in predicting mortality probably because of the interventions in the form of anti-malarial drugs and organ support. Trend in APACHE II and inclusion of parasite count incorporated with seven organ dysfunction severity score can possibly perform better as a malaria severity assessment tool.

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