Original Research Article

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

ABSTRACT

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

Materials and Methods: This longitudinal study was carried out after getting necessary ethics committee approval. Score of APACHE II on days 0, 2nd and 7th were evaluated and appropriate statistical tests were applied.

Results: Out of 120 patients, 54 patients were of P.vivax, P.falciparum - 60 and six mixed infection patients. 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 score of APACHE II on day 2 - cut-off $\geq$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: The prognostic score APACHE II was discovered to be helpful in patients with severe falciparum/vivax malaria who required intensive care treatment since the second day's sequential score significantly differentiates between survivors and non-survivors. The optimum cut-off for identifying individuals at high risk of mortality is 14, and the Day-2 APACHE II score is an ideal biomarker for predicting the outcomes of ICU patients.

Recommendation: Malaria is a major cause of tropical sepsis in India leading to significant amount of mortality. Sequential APACHE II scoring instead of single time APACHE II score calculated on admission could have a role in evaluation of effectiveness of treatment, trend in recovery or dysfunction and prediction of mortality.

Key words: 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 isone 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 seeksevaluate the role of this score in predicting ICU deaths.

MATERIALS AND METHODS: This study was carried out in Vadodara, Gujarat, at a rural teaching hospital. After receiving approval from the institutional ethics committee, the study was carried out. The study included patients who met the inclusion and exclusion criteria and were admitted to the ICU and critical ward.

APACHE II by Wilairatana et al [14,15]

APACHE-II (Acute Physiology and Chronic Health Evaluation) score is more popularly applied in patients of acute critical illness. APACHE II score is the sum of the acute physiology score (vital signs, oxygenation, laboratory values), Glasgow coma score, age and chronic health points. Wilairatana et al in Bangkok, Thailand applied this score to stratify the prognosis in patients of cerebral malaria. With the cutoff point at a score of 19, the APACHE-II stratified the patient's mortality outcome with 95.8% accuracy. This appears to be most sensitive but with low specificity[14,15].

Inclusion criteria:

- The patients in the current study had severe malaria, which was characterised as having multiple organ involvement and smear positive malaria. These patients were

admitted to the ICU and emergency room. Individuals with vivax and falciparum malaria were both included.

Exclusion criteria:

- Patients whose blood tests or assessments that were necessary for APACHE II scoring, such as the serum creatinine, Glasgow Coma Scale (GCS), blood glucose, blood urea, serum bilirubin, urine output, platelet count, haemoglobin and total leucocyte count, could not be properly recorded were excluded from the study.
- Patients under the age of 18 were also excluded.

Between the research periods, 120 total patients willing and met inclusion and exclusion criteria and were available were taken. Out of these patients, 30 were admitted to emergency room and 90 to the ICU. 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 [16,17].

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

The score was calculated on the day of admission, day two, and day seven. Patients division was done in two groups namely "non-survivors" and "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, from 0 to 1 sensitivity plotted on the Y axis and specificity was similarly plotted on the X 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. Two population proportions were tested using the t-test, and categorical values were tested using the chi-square test. ROC curves were plotted by calculating specificity and sensitivity 1, i.e. Use of a pivot table in an Excel spreadsheet to calculate the false-positive rate using the worst APACHE II data for the first seven days and deaths. It was determined what the area under the receiver operating curve (AUROC) was.

RESULTS-86 of the 120 patients were men and 34 were women. There were two groups created: the'survivors' group, which included 82 patients, and the 'non-survivors' group, which included 38 patients who passed away. In the first group, there were 60 males and 22 females, whereas in the second group, there were 26 males and 12 females. The mean age of survivors was 38.56±2.27 years, compared to 40.21±5.6 years for non-survivors (p=0.718). Mortality occurred in 18, 15, and 05 people, respectively, out of 54 patients with P. vivax infection, 60 patients with P. falciparum infection, and 6 patients with mixed infection. 20 (16.67%) patients had a parasite count of 1+, 40 (33.33%) had a count of 2+, 48 (40%) had a count of 3+, and 12 (10%) had a count of 4+.One to two plus parasite counts were present in 56 patients in the survivor group and four in the non-survivor group, while three to four plus parasite counts were present in 26 survivors and 34 non-survivors. The number of parasites (of 3+ and 4+) was statistically larger in patients who died than in survivors (p-value = 0.0031). The three days' average APACHE II scores were calculated. Mean APACHE II values for non-survivors were 18.9474 and 17.8947 on days 0 and 2, respectively, while they were 11.0488 and 10.2927 for survivors. On day 7, the mean for the non-survivor group was 16.1579, while the mean for the survivor group was 8.7073.As can be seen, the mean APACHE II decreased over the course of the disease in both groups. Non-survivors had greater levels of APACHE II than survivors.

ROC curve for the APACHE II score on Day 0 (Fig. 1) reveals that the threshold on the curve that is near to the plot's upper left corner corresponds to a score of 19. As a result, higher discriminant ability was found with an APACHE II score of ≥19. The mean APACHE II score for non-survivors was 18.94, while it was 11.0488 for survivors. As a result, the day 0 APACHE II score provided a prediction approaching cut-off value of ≥19. With a 95% confidence interval (0.7234-0.9618), the AUROC was 0.8426±0.0596 (p=0.013).

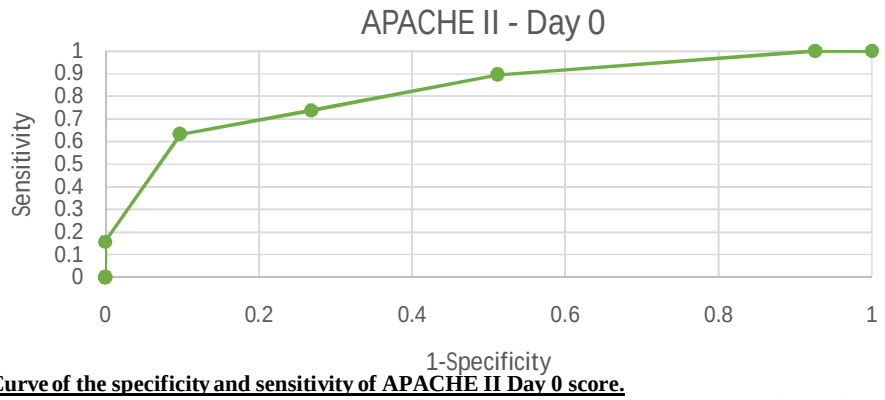

Fig1: Curve of the specificity and sensitivity of APACHE II Day 0 score.
The true positive rate (sensitivity) is represented as a function of the false positive rate (specificity) for various cut-off points in a Receiver Operating Characteristic (ROC) curve. The sensitivity/specificity pair associated with each point on the ROC curve corresponds to a specific decision threshold. The upper left corner of the ROC curve (100% sensitivity and 100% specificity) is crossed by a test with perfect discrimination (no overlap between the two distributions), in this case an APACHE II score of ≥19. As a result, the greater the overall accuracy of the test, the closer the ROC curve is to the upper left corner. With a 95% confidence interval (0.7234 - 0.9618) and this ROC curve has an area of 0.8426±0.0596(p-value =0.013).

ROC curve for the APACHE II score on Day 2 (Fig. 2) reveals that the threshold on the curve that is close to the plot's upper left corner corresponds to a score of ≥14. As a result, higher discriminant ability was found with an APACHE II score of ≥14. The mean APACHE II score for non-survivors was 17.8947, whereas it was 10.2927 for survivors. Hence, the day two APACHE II score provided a prediction reaching cut-off value of 14. With a 95% confidence interval (0.7528–0.9452), the AUROC was 0.8490±0.0481 (p=0.019).

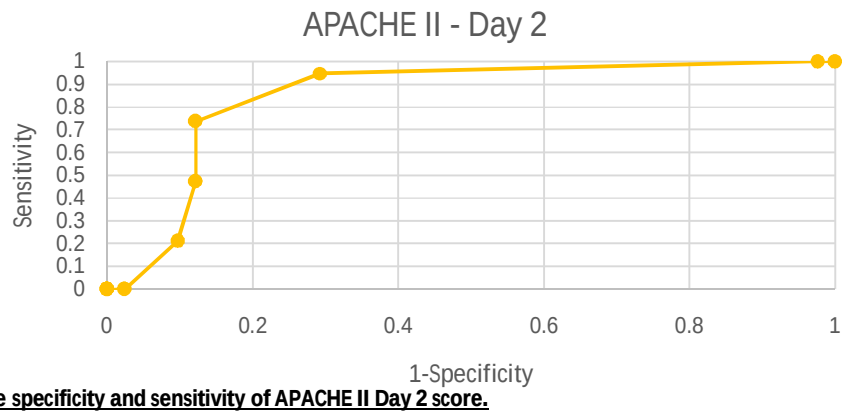

Fig2:Curve of the specificity and sensitivity of APACHE II Day 2 score.
The true positive rate (sensitivity) is represented as a function of the false positive rate (specificity) for various cut-off points in a Receiver Operating Characteristic (ROC) curve. The sensitivity/specificity pair associated with each point on the ROC curve corresponds to a specific decision threshold. The upper left corner of the ROC curve (100% sensitivity and 100% specificity) is crossed by a test with perfect discrimination (no overlap between the two distributions), in this case an APACHE II score of ≥14. As a result, the greater the overall accuracy of the test, the closer the ROC curve is to the upper left corner. With a 95% confidence interval of 0.7528 to 0.9452 and an area of 0.84900.0481, this ROC curve has a p-value of 0.019.

ROC curve of Day 7 APACHE II score (Fig. 3) demonstrates that a threshold on the curve close to the upper left of the plot corresponds to an APACHE II score of14. As a result, higher discriminant ability was found with an APACHE II score of ≥14. Mean APACHE II was 16.1579 in the non-survivor group and 8.7073 in the survivor group. As a result, the prediction attaining cut-off value for day 7 of APACHE II was ≥14. With a 95% confidence

interval (0.6659-0.9003), the AUROC was 0.7831±0.0586 (p = 0.013).

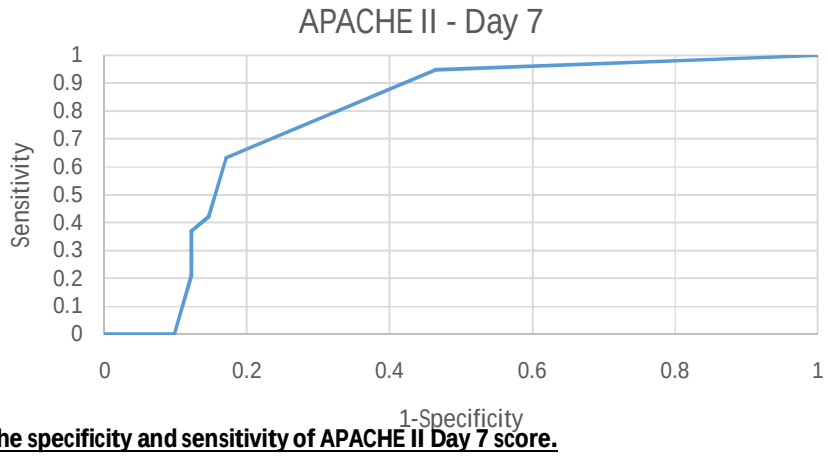

Fig3:Curve of the specificity and sensitivity of APACHE II Day 7 score.
The true positive rate (sensitivity) is represented as a function of the false positive rate (specificity) for various cut-off points in a Receiver Operating Characteristic (ROC) curve. The sensitivity/specificity pair associated with each point on the ROC curve corresponds to a specific decision threshold. The upper left corner of the ROC curve (100% sensitivity and 100% specificity) is crossed by a test with perfect discrimination (no overlap between the two distributions), in this case an APACHE II score of ≥14. As a result, the greater the overall accuracy of the test, the closer the ROC curve is to the upper left corner. With a 95% confidence interval (0.6659 - 0.9003), this

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 score of APACHE II had maximum predictive value on day 2 for mortality due to malaria.

Table:1-Comparing APACHE II scoring system on Days 0, two and seven 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

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

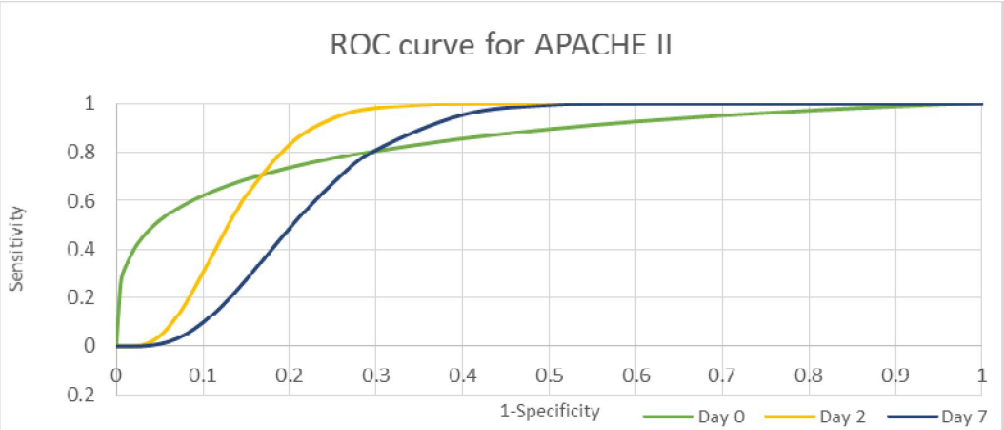

Fig4:Curve of the sensitivity and specificity of APACHE II Day 0 (Green), 2 (yellow) and 7 (Blue) score.

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 other six diseases (HIV/AIDS, pneumonia,diarrhoea, hepatitis B,tuberculosis andmeasles), malaria accounts for 85% of the burden of infectious diseases worldwide and imposes a major socioeconomic burden on society[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.

36% of the world's population, or about 2020 million people, are susceptible to contracting malaria. The World Health Organization estimates that malaria affects 300–500 million people worldwide each year, with 90% of those cases happening 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. Concerns have

been raised over the accuracy of these estimates because to the lack of trustworthy diagnostic facilities and reporting systems in the majority of hyper- and holoendemic states, notably in Africa [5, 6]. In the WHO's Southeastern Asia Region, 6% of the world's population—or1.2 billion people —who live in eleven countries and number 1.4 billion—are at risk of developing 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 twenty countries in Sub-Saharan Africa and India were responsible for the majority of malaria-related deaths worldwide, 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 risk factor identification could reduce malaria-related morbidity and mortality as delayed diagnosis is one of the major risk factors for 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 MODS - Multi Organ Dysfunction Syndrome [12].Malaria caused by P. vivax can result in death, cause multiple organ failure and thrombocytopenia, and be severe and resistant, similar to malaria caused by falciparum species[13]. The prognosis of a patient is evaluated in an ICU setting using a variety of grading techniques. Simplified Acute Physiology Score (SAPS), Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) scoreand others are a few of the techniques [12,13,16].A general classification method for disease severity is called APACHE II. In order to offer a general assessment of disease severity, APACHE II derives a point score based on the beginning values of 12 common physiologic measures, age, and prior health condition. In a study similar to ours, Knaus WA et al discovered that an increasing score (ranging from 0 to 71) was closely connected with the likelihood of hospital death that followed[11]. Aim of the

present research was applicability of APACHE II scoring system in a rural population catering tertiary care teaching hospital. Medical care is required for the clinical problem of malaria, which is frequently seen. The goal of the current study was to determine whether sequential APACHE II scoring was applicable to patients with vivax and/or falciparum malaria who were admitted to critical care wards. In this investigation, parasite count was a crucial metric; patients with higher parasite densities had a higher probability of dying. Non-survivors had a considerably higher prevalence of admission parasite counts of 3 to 4 plus than survivors. For each of the days of admission, the APACHE II score was considerably higher among non-survivors. While the trend of APACHE II can predict death on further follow-up, parasite count can also be an effective prognostic marker for early risk assessment of mortality and morbidity/MODS. Ali H et al conducted a study in Karachi, it was discovered that a high parasite density was linked to severe clinical disease, complications, and mortality[17]. In this investigation, the fatality rates for both vivax and falciparum strains were nearly comparable. 38 patients passed away and 82 were still alive. In a group of 54 patients with P. vivax, 36 patients survived and 18 patients passed away, whereas in a group of 45 patients with falciparum malaria, 15 patients passed away. Five of the six individuals with combined infections passed away. In the current study, non-survivors' mean APACHE II scores on days 0, 2, and 7 were greater than those of survivors. The APACHE II score from day two demonstrated similar specificity to the day 0 score and maximal sensitivity and negative predictive value.Thus day 2 APACHE II score with maximum AUROC and had maximum predictive value for in hospital mortality.If organ support therapies and anti-malarial therapy were successful, a declining/stationary trend in scores was seen. Consequently, it can be inferred that the scores rise when anti-malarial medications don't work as well (drug resistance or presence of dysregulated host response to malaria). Serial scoring may exhibit an upward or downward trend, according to the current study, and is a

better prognosis indication than a single severity assessment. In a comparable study, serial measurement of the SOFA score on the third to seventh day (first week) was found to be a more accurate predictor of sepsis outcomes than the SOFA score and APACHE-II score on day 0 (on admission) [11]. While MSS is a disease-specific score, it does not account for "Age" and "Related co-morbidities" like APACHE does when predicting the probability of death from malaria. APACHE is not disease-specific and considers other host factors like "Age" and "Co-morbidities." Age did not significantly differ between the groups of survivors and non-survivors in the current investigation. Comparing APACHE II sequential measurement to a single score measurement can be advised. As parasite count is a precise predictor of the severity of malaria, it can be included in the prognostic scoring system[18]. A novel, definite and specific severity and prognostic scoring system model, developed through prospective research, is still required in order to accurately forecast the course of each patient with 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 [19].

CONCLUSION(S): The APACHE II scoring system has been found to be a helpful prognostic score in cases of severe falciparum/vivax malaria that require intensive care treatment. Sequential scores provide a significant difference between survivors and non-survivors on all days, while parasite counts on the day of admission can be a good indicator of mortality on that day.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.As a technique for determining the severity of malaria, the APACHE II

trend and inclusion of the parasite count along with the severity score for each of the seven organ dysfunctions may perform better.

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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