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Comparison of Severity of Illness Scoring Systems in the Prediction of Mortality among Patients with Severe Sepsis and Septic Shock - A Prospective Observational Study

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Abstract: ***Background: Sepsis, which can progress to severe sepsis and septic shock, is becoming a major healthcare problem and affects millions of people around the world each year. Sepsis and septic shock result in mortality rates of one in three and one in six affected patients, respectively. Early identification and appropriate management improve outcomes. It is equally essential to compare various scoring systems to determine which combination of parameters best predicts the outcome of the patient. Aim: To determine which among APACHE II and MEDS is better in predicting in-hospital mortality among patients with severe sepsis and septic shock. Objectives: 1) To compare APACHE II and MEDS score in the prediction of hospital mortality among patients with severe septic and septic shock treated with MEGDT. 2) To assess the ability of APACHE II and MEDS score to predict mortality among patients with severe sepsis and septic shock treated with Modified Early Goal Directed Therapy. Design, Setting, and participants: A prospective observational study was conducted at KIMSHEALTH Thiruvananthapuram from December 2020 to June 2022, involving 116 sepsis patients over 18 years. Method: APACHE II and MEDS scoring were done for the study population, and results were compared to determine sensitivity and specificity. Results: Measurement of MEDS score and APACHE II score on 1st day of admission for scoring severity of illness had good predictive capability for mortality. While MEDS and APACHE II scores exhibited equal specificity, the sensitivity of APACHE II was 100 % compared to 97.6 % for MEDS. Conclusion: Measurement of both MEDS score and APACHE II score on the day of ED admission is a very useful tool in predicting the outcome among sepsis and septic shock patients. The APACHE II score demonstrated the largest AUC of the studied scoring systems and showed slightly better sensitivity, PPV, NPV and accuracy than MEDS score, although both shared equal specificity.***

Keywords: Sepsis, Septic shock, APACHE II score, MEDS

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This new definition emphasizes the primacy of the nonhomeostatic host response to infection, the potential lethality that is considerably in excess of a straightforward infection, and the need for urgent recognition. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. (1)

Sepsis was previously defined and identified using Systemic Inflammatory Response Syndrome criteria (SIRS -Two or more of: Temperature >38°C or <36°C, Heart rate >90/min, Respiratory rate >20/min, White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands). However, SIRS has been criticized for its low specificity, which led to the introduction of the quick Sequential Organ Failure Assessment (qSOFA-Two or more of:

Respiratory rate ≥22/min, Altered mentation, Systolic blood pressure ≥100 mm Hg) proposed by the third international consensus definition (Sepsis-3). (1)

qSOFA Score: qSOFA has better specificity but lower sensitivity than SIRS. Consequently, it might not detect patients early and may not be beneficial for ED utilization. (2) Sepsis is a critical condition with a high mortality rate and is

considered a major health problem worldwide. (3) Globally, 31.5 million cases of sepsis are reported annually, with an estimated mortality of 5.3 million. In high-income countries, around 20 million people suffer from sepsis each year with mortality rate ranging between 17 and 26%. (4)

Sepsis is treatable, and timely implementation of targeted interventions improves the outcome. Infection prevention efforts, targeting community acquired and health-care-associated infections, can reduce sepsis incidence. (5)

Early administration of antibiotics is also associated with better survival, thus screening and early detection for sepsis is of clinical importance. (6) Numerous scores that have been devised both for detection and prognostication of sepsis have also led to sepsis alert systems in which patients considered to be at high risk of critical illness are prioritized and treated according to sepsis bundles. (7)

Each scoring system uses a different combination of parameters to stratify the patient. Hence, it is vital to compare various scoring systems to find out which combination of parameters best predicts the status of the patient. (8)

For use as a screening tool amongst undifferentiated patients in the Emergency Department (ED), a score should be capable of discriminating sepsis from other competing diagnoses and also predict the development of sepsis among infected patients. (9) The objective of our study is to compare various severity assessment scoring systems, namely Acute Physiology and Chronic Health Evaluation II (APACHE II), and Mortality in Emergency Department Sepsis (MEDS).

Compared with the APACHE II, the APACHE III is more complex and time-consuming. (10)

The mortality in emergency department sepsis (MEDS) score was derived and validated in patients presenting to the ED with suspected sepsis, and includes basic demographic, clinical, and laboratory variables obtained during a patient‟s time in the ED, which are weighted to give a final score and mortality risk assessment. (11)

We restrict our analysis to ED patients treated with our hospital's Modified Early Goal Directed Therapy Protocol (MEGDT). Components of our hospital protocol include the early administration of fluids and antibiotics (within one to six hours) using the following targets to measure the response: mean arterial pressure (MAP) >65 mmHg, and urine output >0.5 mL/kg/hour. (12)

2. Literature Survey

Sepsis, which can progress to septic shock, is becoming a major healthcare problem and affects millions of people around the world each year. Sepsis and septic shock are killing one in three and one in six of those it affects.[4] Early identification and appropriate management improve outcomes. It is equally essential to compare various scoring systems to determine which combination of parameters best predicts the outcome of the patient. "The Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021" offers recommendations to guide clinicians. These are intended to reflect best practices.

Definition of Sepsis and Septic Shock:

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[13] Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction. A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.

Table 1: SOFA score indices for individual organ dysfunction.[1]

Lung	PaO_2/FIO_2<400
Liver	Serum bilirubin ≥1.2 mg/dl
Kidney	Serum creatinine ≥1.2 / Urine output <500 ml/day
Cardiovascular system	Mean arterial pressure <70 mmHg
Central nervous system	Glasgow Coma Scale (GCS)<15
Blood coagulation system (Disseminated intravascular coagulation)	Platelets $<150 \times 10^3/\mu l$

Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a MAP of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[14]

Sepsis Pathophysiology

Multifaceted disruption of the finely tuned immunological balance of inflammation and anti-inflammation. The upregulation of pro- and anti-inflammatory pathways lead to a system-wide release of cytokines, mediators, and pathogen-related molecules which results in activation of coagulation and complement cascades. [15]

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Screening and Early Treatment

Sepsis performance improvement programs consist of sepsis screening, education, measurement of sepsis bundle performance, patient outcomes, and actions for identified opportunities.[16] Despite some inconsistency, a meta-analysis of 50 observational studies on the effect of performance improvement programs showed that these programs were associated with better adherence to sepsis bundles along with a reduction in mortality in patients with sepsis and septic shock.[17]

Sepsis screening tools are designed to promote early identification of sepsis and consist of manual methods or automated use of the electronic health record (EHR). There is wide variation in diagnostic accuracy of these tools with most having poor predictive values, although the use of some of these were associated with improvement in patient care. A variety of clinical variables and tools are used for sepsis screening, such as systemic inflammatory response

syndrome (SIRS) criteria, vital signs, signs of infection, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS).[18]

Machine learning may improve performance of screening tools, and in a meta analysis of 42,623 patients from seven studies for predicting hospital acquired sepsis, the pooled area under receiver operating characteristic curve (AUROC), sensitivity and specificity were higher for machine learning than the AUROC for traditional screening tools such as SIRS, MEWS, and SOFA.[19]

Sepsis and septic shock are medical emergencies, and thus treatment and resuscitation should begin immediately. For adults with septic shock on vasopressors, an initial target mean arterial pressure (MAP) of 65mm Hg is recommended over higher MAP targets. Antimicrobials should be administered immediately, ideally within 1 hr of recognition. Empiric antimicrobials with MRSA coverage is recommended over using antimicrobials without MRSA coverage for patients at high risk for MRSA. Crystalloids are recommended as first-line fluid for resuscitation and norepinephrine as the first-line agent over other vasopressors.

For adults with sepsis-induced ARDS, low tidal volume ventilation strategy (6 mL/kg) and plateau pressures of 30 cm H2O are recommended over a high tidal volume strategy (>10 mL/kg) and higher plateau pressures respectively. When using recruitment maneuvers, the guidelines recommend against using incremental PEEP titration/strategy. Prone ventilation for greater than 12 hours daily is recommended. Pharmacologic venous thromboembolism (VTE) prophylaxis should be used unless a contraindication to such therapy exists and low molecular weight heparin is preferred over unfractionated heparin.[14]

Early Goal Directed Therapy (EGDT):
EGDT has been introduced as an interesting approach characterized by early recognition and prompt initiation of a structured treatment algorithm. EGDT targeted a CVP >8 mmHg, a MAP >65 mmHg, a diuresis >0.5 mL/kg/hour and a Central Venous Oxyhemoglobin Saturation > 70%.[20]

Modified Early Goal Directed Therapy:
The primary goal of the cohort study conducted by Hanzelka K et.al was to implement a non-invasive sepsis EGDT management protocol in the emergency center. The algorithm focused on early identification at triage based on vital signs, timely laboratory evaluation including point-of-care lactic acid measurement, timely administration of antibiotics and aggressive resuscitation with intravenous normal saline. Patients whose blood pressure did not normalize or who had an elevated lactic acid level of ≥4 mmol/L were entered into the septic shock arm of the algorithm. Vasopressor therapy consisting of either norepinephrine or dopamine was initiated immediately for MAP < 65 mmHg that persisted after the hydration goal of > 20 mL/kg was achieved.

The results of this trial indicate that implementation of an order set and algorithm for the treatment of sepsis and septic shock using a non-invasive implementation of EGDT is associated with improved 28-day in-hospital mortality. Elevated serum lactate (≥4 mmol/L) independent of organ failure and failure to clear lactate during early resuscitation are both associated with an increase in mortality. (12)

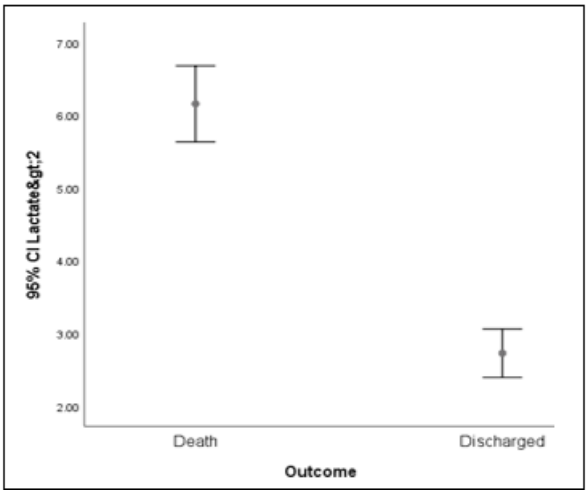
3. Materials and Methods

The research was carried out in the department of Emergency Medicine, KIMSHEALTH, Trivandrum during December 2020 to June 2022. Patients suffering from severe sepsis and septic shock admitted in the Emergency department of KIMSHEALTH, Trivandrum above the age of 18 years and who had given consent are included in the study. Patients with comorbidities such as End stage cardio pulmonary disease, Chronic liver disease, Poorly controlled neoplasms, HIV positive cases with known end stage processes were excluded from the study. Accordingly, 116 patients were included in the study.

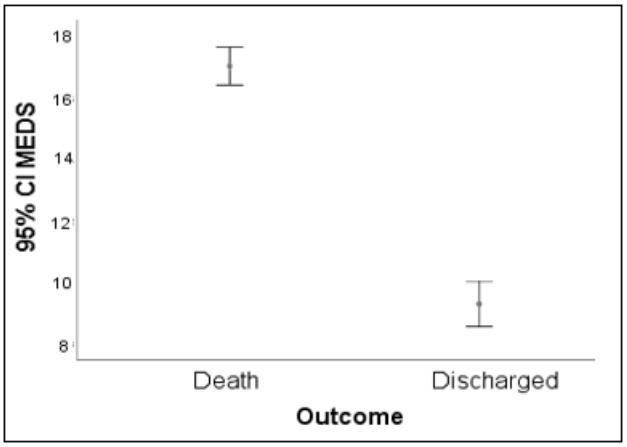
Method of Measurement of Outcomes
The socio-demographic data, clinical history including past history, family history, personal history were collected from the Electronic Medical Record, patient and relatives. Results or data on clinical examination including vitals, GCS score, general examination and systemic examination with detailed examination of cardiovascular, renal and respiratory systems were obtained from the EMR. Patients were treated as per the hospital protocol on modified early goal directed therapy for sepsis and septic shock; APACHE II and MEDS scoring were done as a routine examination in these sick patients. Patients were followed up till an event of death or discharge from hospital within 28 days of admission to hospital.All collected data were entered into structured proforma and analyzed using appropriate statistical methods. The primary endpoint was the comparison between APACHE II and MEDS scoring systems and finally coming to the conclusion about which scoring system best predicts 28 days hospital mortality and thus helped in classifying patients into survivors and non survivors.

4. Results

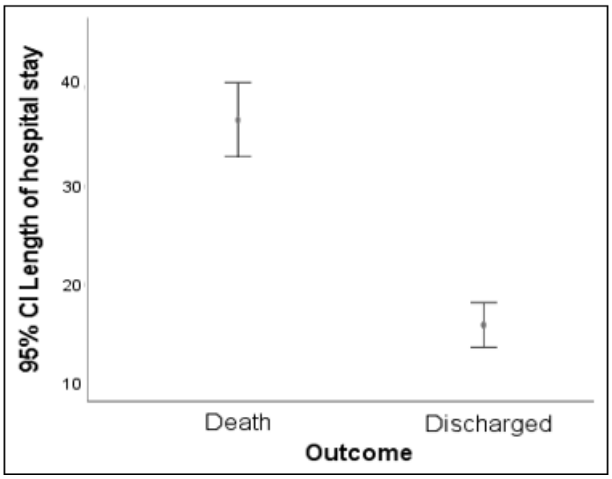
Comparison of Lactate among Survivors and Non Survivors



Comparison of Meds Score among Survivors and Non-Survivors

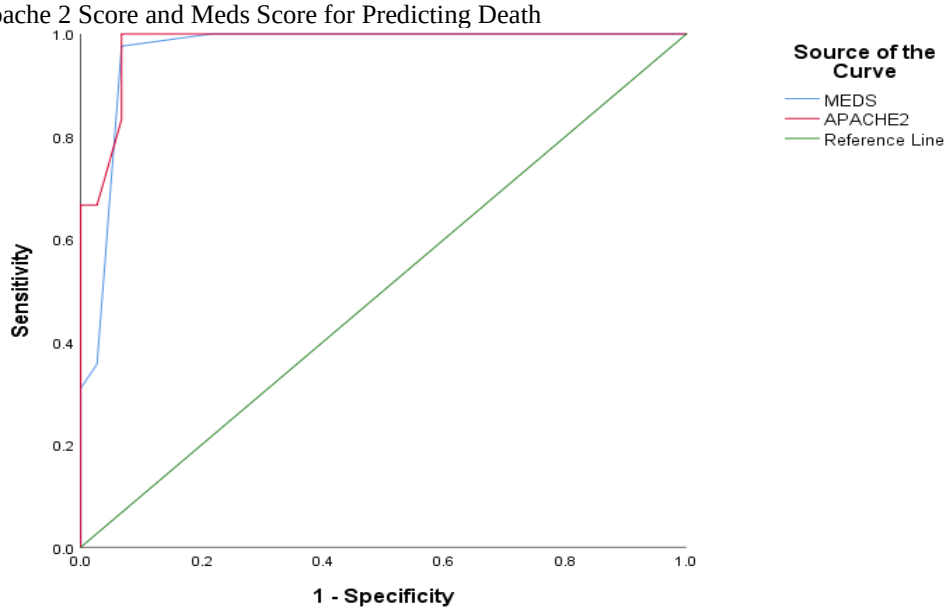


Comparison of Length of Stay among Survivors and Nonsurvivors



Comparison of Apache 2 Score among Survivors and Non Survivors

ROC Curve of Apache 2 Score and Meds Score for Predicting Death



Area under the ROC curve of APACHE 2 score and MEDS score for predicting death

Variable	P value	Area	95% Confidence Interval
MEDS score	<0.001*	0.967	0.936-0.998
APACHE 2 score	<0.001*	0.981	0.962-1.000

Diagnostic characteristics of APACHE II score and MEDS score for predicting death

Variable	Cut-off score	Sensitivity	Specificity	PPV	NPV	Accuracy
MEDS score	≥14.50	97.6	93.2	89.1	98.6	94.8
APACHE 2 score	≥28	100	93.2	89.4	100	95.7

5. Discussion

Around 116 patients diagnosed with sepsis and septic shock in our Emergency Department during the study period satisfied the inclusion criteria and were enrolled for the study and none of the exclusion criteria were included. After obtaining informed consent, each patient's socio demographic characteristics, vital parameters, laboratory and radiological parameters were studied. MEDS and APACHE II scoring were also done for all the participants and were treated with modified EGDT.

a) Baseline Characteristics:

In our study, 42 patients died and 74 patients survived for an in-hospital 28 day mortality of 36.2 %, which was lesser than the overall mortality of 55.9% in the study done by Bhadrinath K et al.[3] This may be attributed to the usage of MEGDT in our study. Hospital mortality was 17% for sepsis and 26 % for severe sepsis in the study done by Fleischmann et al[4], which was almost similar to our study. Men were shown to be more likely to suffer from sepsis in our study which consisted of 63 males and 53 females. This was consistent with the study of Bhadrinath K et al[8], where percentage of males was 64.76% and with the study of Angels M et.al.[33] After analysis, it was found that 80 patients were above 60 years, only 9 patients were below 40 years and the rest of them were between 40 and 60 years. Old age with its associated comorbidities also predispose these patients to sepsis. This was supported by the studies conducted by Martin G et.al[34] and Badrinath K et.al.[8] In our study, the majority of patients suffered from respiratory pathology - 37.1 %, followed by GIT causes - 25 %, and urological causes - 21.6 %. Martin G also concluded that respiratory infections accounted for almost half of the sepsis patients. Similar other studies corroborate that although most common site of infection was GIT, mortality was higher among patients with respiratory pathology.[35] Blood gas analysis of the majority of patients showed a metabolic acidosis - 60.3 %, while 25.8 % showed respiratory acidosis, 0.86 % showed metabolic alkalosis and 1.7 % showed respiratory alkalosis. 28.4 % have a normal ABG. The mean value of lactate in our study was 3.96 which was statistically significant. The mean value of MEDS and APACHE II score were 12.09 and 23.5 respectively.

b) Primary Outcome Measures:

Primary aim was to compare between the ability of APACHE II and MEDS score in predicting mortality among patients with severe sepsis and septic shock treated with Modified Early Goal Directed Therapy. The cut-off score for predicting mortality of MEDS score was >14.5 and that of APACHE II score was >28 in our study. This was comparable with the Singaporean cohort study conducted by Pong et.al, where the cut-off score of MEDS score was >12 and that of APACHE 2 was > 23.[36] The mean MEDS score in our study among non survivors was 17.05 and survivors was 9.28, which was comparable with the similar study conducted by Shameem KU, where the mean MEDS score was high among non-survivors than survivors (16.31 vs 9.15).[37] The mean APACHE II score among non survivors was 34.5 and survivors was 17.26. These values were comparable with the study conducted by M Hosseini and J Ramazani, where the mean APACHE II score for nonsurvivors was 21.02 ± 6.71 compared with 14.93 ± 6.02 for survivors.[38] The area under the ROC curve for predicting mortality of MEDS was 0.967 with a 95% confidence interval of 0.936-0.998 while that of APACHE II was 0.981 with CI of 0.962-1.000. This was slightly lower than the study conducted by ShengTao Yan and GuoQiang Zhang, where the AUROC of MEDS was 0.761 and that of APACHE II was 0.778.[39] Both the scores were statistically significant with a p value of <0.001. The specificity of both the scores were 93.2, while APACHE II score showed a slightly better sensitivity, PPV, NPV and accuracy. This was in accordance with similar studies done by Bhadrinath et al[8] and APACHE II showed higher sensitivity as it takes into account, age, surgical status of patient, comorbidities, temperature, blood pressure, serum creatinine, sodium and potassium as compared to MEDS. While MEDS assigns a score based on presence or absence of organ failure, APACHE II assigns a score to each of the parameters depending on how far they vary from the normal value, thus interpreting the severity of organ failure.

c) Secondary Outcome Measures (Clinical Predictors of Mortality)

1) **Age:** All sepsis patients that belonged to the age group: < 51 years survived the illness and this was statistically significant with a p value of 0.001. There are high mortality rates of around 50-60% in elderly patients with severe sepsis and septic shock according to the study conducted by Martin G et al.[34]
2) **Sex:** Both the number of sepsis patients and number of deaths were more among male gender than female gender but this was not statistically significant with a p value of 0.104. Epidemiological studies demonstrate gender differences with respect to the development of septic complications and multiple organ failure. In this respect, Offner et al. identified the male gender as an independent risk factor for development of severe infection in surgical patients. Low dihydrotestosterone and / or high estradiol appear to be protective for the females following an adverse circulatory condition like septic shock.[33,40]
3) **Etiology:** Respiratory infections account for approximately half of all cases of sepsis overall. The next most common causes are genitourinary and abdominal sources of infection while primary bacteremia and unknown sources are the next most common causes. The occurrence of acute organ dysfunction is again related to the source of infection, like in patients with respiratory infections who are at greater risk for developing respiratory organ dysfunction.[41]
4) **Vital parameters:** The mean MAP value among non survivors and survivors were 58.39 and 68.4 respectively, and this was statistically significant with a p value of <0.001. The risk of mortality is conditionally dependent on MAP, which was shown to be

independently associated with mortality in sepsis. This result is comparable with Ribas et al [42] and Gultepe E et al.[43] Patients with natural hypothermia showed a higher risk of death compared with those with fever. Thus excessive temperature control may also be harmful to septic patients.[44] The mean value of GCS among non survivors was 11.2 and survivors were 14.41 and this was statistically significant with a p value of <0.001. GCS was identified as a substantial risk factor in the study conducted by Chen SH et al.[46]

5) **Laboratory parameters:** Laboratory parameters such as Leukocytosis, Thrombocytopenia, elevated ESR, Hyponatremia, Hyperbilirubinemia, elevated blood urea nitrogen, Creatinine and lactate were found to be significantly associated with increased morbidity and mortality. This was strongly in accordance with other similar studies conducted by Chen SH et al[46] and Shapiro et al[11].

6. Conclusion

To conclude, findings of our study suggest that measurement of both MEDS score and APACHE II score on the day of ED admission is a very useful tool in predicting the outcome among sepsis and septic shock patients. The APACHE II score demonstrated the largest AUC of the studied scoring systems and showed slightly better sensitivity, PPV, NPV and accuracy than the MEDS score, although both shared equal specificity. Male sex and older age were predominant in our study population which is reflected in other similar studies also. Our study also suggests that respiratory infection is one of the most common etiology of sepsis and also has a grave prognosis. We found that measurement of MAP, temperature, Spo2, Glasgow coma scale and other laboratory parameters like WBC count, PLC count, ESR, Sodium, Total bilirubin, BUN, Creatinine and lactate on the day of ED admission are independent predictors of mortality.

7. Future Scopes

One of the primary limitations in our study is a small sample size as a larger sample size could have better validated the scoring system. The data collected for both the scores were done only at the day of presentation to the emergency department, hence the trend in the results could not be identified. Our study was conducted in only two departments and that too in a single center. A multicentric study may be necessary for conclusive results.

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