Dynamic APACHE II Score to Predict Outcome Among Intensive Care Unit Patients

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Research

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Abstract

Purpose: The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is used to determine disease severity and predict outcomes in critically ill patients. However, there is no dynamic APACHE II score for predicting outcomes among ICU patients. The aim of this study is to explore the optimal timing to predict the outcomes of ICU patients by dynamically evaluating APACHE II score.

Methods: Study data of demographics and comorbidities from the first 24 h after ICU admission were retrospectively extracted from MIMIC-III, a multiparameter intensive care database. The primary outcome was hospital mortality. 90-day mortality was a secondary outcome. APACHE II scores on days 1, 2, 3, 5, 7, 14 and 28 were compared using area under the receiver operating characteristic (AUROC) analysis. Hospital survival was visualised using Kaplan-Meier Curves.

Results: A total of 6374 eligible subjects were extracted from the MIMIC-III. Mean APACHE II score on day 1 were 18.4 ± 6.3 , hospital and 90-day mortality was 19.1% and 25.8%, respectively. The optimal timing where predicted hospital mortality was on day 3 with an area under the curve of 0.666 (0.607-0.726) ($P < 0.0001$). The best tradeoff for prediction was found at 17 score, more than 17 score predicted mortality of non-survivors with a sensitivity of 92.8% and PPV of 23.1%. Hosmer-Lemeshow goodness of fit test showed that APACHE II 3 has a good predictive calibration ability ($\chi^2 = 6.198$, $P = 0.625$) and consistency of predicted death and actual death was 79.4%. The calibration of APACHE II 1 was poor ($\chi^2 = 294.898$, $P < 0.001$).

Conclusions: APACHE II on 3 days is the optimal prognostic marker and 17 score provided the best diagnostic accuracy to predict outcomes for ICU patients. These findings will help medical make clinical judgment.

Introduction

Predicting ICU mortality plays an important role in patient care and resource allocation. Early identification and management are associated with lower mortality [1, 2]. At present, there are many predictive scoring systems including Acute Physiology Chronic Health Evaluation II (APACHE II), Organ Dysfunction and Infection System, Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score (SAPS) for hospital outcomes [3–5], especially for mortality [6, 7]. Among which APACHE II score is the most common and well-known effective prediction scoring method. At present, most studies use the APACHE II score within 24 h of admission to predict the outcomes of patients [2, 8]. However, for the first 24 h of ICU admission, many patients have several comorbid conditions, and selecting only one principal diagnostic category may be very difficult. Moreover, the condition of patients was unstable and their physiological indexes fluctuated greatly. All these factors had a great impact on APACHE II score within 24 h, which leads to inaccurate prognosis of hospital outcomes. In addition, Evaluation criteria are usually based on the area under receiver operating characteristic (ROC) curve, which may not be enough to guide the decision on which model is the best. Good of fit testing is another

factor that should be considered. Therefore, it is very significance to explore the optimal timing for APACHE II score by dynamically evaluating the APECHE II score and verify its calibration.

Methods

Date source

This study based on Medical Information Mart for Intensive Care (MIMIC) III (Philips Healthcare, Andover, MA; and Beth Israel Deaconess Medical Center) ICU database, which is large, publicly available database compromising the clinical diagnosis and treatment information of approximately 46,000 critically ill patients admitted to the Beth Israel Deaconess Medical Center (Boston, Massachusetts) from 2001 to 2012[9–11]. We obtained approval to access the database(Certification Number: 36379199) after completing the National Institutes of Health web-based training course“Protecting Human Research Participants”.

Date Extraction And Management

Two authors independently extracted the relevant date and assessed the eligibility and quality of the study. Date on the following aspects were extracted: age, sex, survival status, admission type, date of ICU and hospital admission and discharge, date of birth and death. The hospital and ICU length of stay (LOS), Patients discharged from hospital or deceased before day 28 were censored to the last known APACHE II score. APACHE II scores was calculated as described in previous studies[12, 13], The days of hospitalization were calculated by subtracting the time of admission from the time of discharge. To safeguard patient privacy, date were deidentified[14], therefore, The days of death after discharge were calculated by subtracting the date of discharge from the date of death of each patient, and the 90-day mortality was further calculated. Only the first diagnosis was selected as the object of date analysis, and the disease classification was gradually refined according to the *International Classification of Diseases-9th* (ICD-9) edition comorbidities[15], Serial APACHE II scores were calculated on days 1,2,3,5,7,14 and 28 after enrollment in ICU. The primary endpoint was hospital mortality. The secondary endpoints was 90-day mortality, For patients younger (> 18 year old) readmitted to the ICU, only the first ICU admissions were included. Date were extracted from the following tables(ADMISSIONS,ICUSTAYS, PATIENTS, CHARTEVENTS, LABARARY EVENTS and DIAGNOSIS_ICD). We excluded patients who were Individuals were exclued if (1)stayed in ICU less than on day; (2) Patients with missing date of APECH II score.

Statistical analysis

Quantitative variables and categorical date are expressed as mean $\pm$ SD and (number and percentage),respectively. Compared between groups using a t-test, if the data were normally distribed and the variance was homogeneous. If not, data were represented by the median and interquaritle range, and the wilcoxon rank-sum test was used for comparisons between groups.Discrimination and

calibration were assessed using the area under the receiver operating characteristics curve (AUROC) and Hosmer-Lemeshow statistic, respectively. We used the Youden Index to estimate the optimal cut off values by finding values that returned the maximum specificity and sensitivity. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed by IBM SPSS Statistics (IBM, Armonk, NY, USA).

Results

Baseline patient characteristics and outcomes

The flow charts is shown in Fig. 1. A total of 46520 patients were including in MIMIC-III database. After including only patients' first ICU admissions and excluding admissions under the age of 18, less than 24 h in ICU and lack of Apache II scores, Finally, 6374 patients were included in this study (Fig. 1). The baseline characteristics and outcomes of patients are summarized in Table 1. The overall mean age was 64.1 ± 16.8 years (63.2 ± 16.7 in survivors Vs 68.4 ± 15.9 in non-survivors), 57.8% was male ($n = 3683$), The difference of demographics between survivors and non-survivors were statistically significant ($P \leq 0.05$). APACHE II on days 1, 2, 3, 5, 7, 14 and 28 were 18.4 ± 6.3 , 15.4 ± 5.8 , 15.9 ± 5.9 , 16.8 ± 5.8 , 17.5 ± 6.3 , 17.6 ± 6.6 and 15.7 ± 6.9 , respectively. The non-survivor group showed higher APACHE II score compared to survivor group at all test points ($P < 0.001$). The hospital mortality and ICU mortality were 19.1% and 15.7%, respectively, ICU and hospital LOS (Length of stay) were 8.62 ± 9.0 and 15.7 ± 13.7 days. Besides, the diseases of circulatory system was listed as the most common diagnosis among 1865 patients (29.3%).

Table 1
Comparative baseline demographics according to survival status

Variables	All (n = 6374)	Survivors (n = 5158)	Nonsurvivors (n = 1216)	P values
Demographics				
Age, mean (SD), year	64.1 ± 16.8	63.2 ± 16.7	68.4 ± 15.9	<i>P</i> < 0.001
Male, No. (%)	3683(57.8)	3019(58.5)	664(54.6)	<i>P</i> = 0.013
APACHII score(SD)				
APACHII on day 1	18.4 ± 6.3	18.0 ± 6.3	19.8 ± 6.1	<i>P</i> < 0.001
APACHII on day 2	15.4 ± 5.8	14.5 ± 5.4	19.6 ± 5.7	<i>P</i> < 0.001
APACHII on day 3	15.9 ± 5.9	14.5 ± 5.2	20.2 ± 5.8	<i>P</i> < 0.001
APACHII on day 5	16.8 ± 5.8	14.9 ± 4.9	20.6 ± 5.7	<i>P</i> < 0.001
APACHII on day 7	17.5 ± 6.3	15.0 ± 5.1	21.6 ± 5.9	<i>P</i> < 0.001
APACHII on day 14	17.6 ± 6.6	14.2 ± 4.8	22.4 ± 5.8	<i>P</i> < 0.001
APACHII on day 28	15.7 ± 6.9	12.4 ± 4.4	23.2 ± 5.6	<i>P</i> < 0.001
Outcomes				
Hospital mortality, No. (%)	1216(19.1)	0	1216(100)	<i>P</i> < 0.001
ICU mortality, No. (%)	1001(15.7)	0	1001(82.3)	<i>P</i> < 0.001
90-day mortality, No. (%)	1648 (25.8)	0	1648 (25.8)	<i>P</i> < 0.001
ICU LOS, median (IQR), d	8.62 ± 9.0	8.5 ± 9.1	9.3 ± 8.9	<i>P</i> = 0.005
Hospital LOS, median (IQR), d	15.7 ± 13.7	16.4 ± 13.8	12.6 ± 12.8	<i>P</i> < 0.001
Diagnoses on Admission to ICU, No. (%)				

Variables	All (n = 6374)	Survivors (n = 5158)	Nonsurvivors (n = 1216)	<i>P</i> values
Infectious and parasitic diseases	619(9.7)	422(8.2)	197(16.2)	<i>P</i> < 0.01
Neoplasms	180(2.8)	135(2.6)	45(3.7)	<i>P</i> < 0.01
Endocrine,nutritional,and metabolic disease and immunity disorders	642(10.1)	560(10.9)	82(6.7)	<i>P</i> < 0.01
Blood and Blood forming organs	568(8.9)	488(9.5)	80(6.6)	<i>P</i> < 0.01
Diseases of nervous system and sense organs	69(1.1)	65(1.3)	4(0.33)	<i>P</i> < 0.01
Diseases of circulatory system	1865(29.3)	1579(30.6)	277(22.8)	<i>P</i> < 0.01
Diseases of respiratory system	982(15.4)	765(14.8)	217(17.8)	<i>P</i> < 0.01
Diseases of digestive system	445(6.9)	369(7.2)	76(6.3)	<i>P</i> < 0.01
Diseases of genitourinary system	657(10.3)	463(8.9)	194(16.0)	<i>P</i> < 0.01
Disease skin and subcutaneous tissue	82(1.3)	67(1.3)	15(1.2)	<i>P</i> < 0.01
Diseases of musculoskeletal and connective tissue	40(0.6)	36(0.7)	4(0.3)	<i>P</i> < 0.01
Injury and poisoning	234(3.7)	209(4.1)	25(2.1)	<i>P</i> < 0.01

Table 2
Prognostic performance for outcomes of the 17 cutoff on ApechII 3 day

APACHII score	Hospital mortality		90-day mortality		
	Non-survivors (n)	Survivors(n)	Non-survivors (n)	Survivors(n)	Total
APACHII $\geq$ 17	928	3081	1213	2796	4009
	Sens:92.8%	Sens:82.2%	Sens:92.2%	Sens:81.3%	
	PPV: 23.1%		PPV:30.3%		
APACHI < 17	288	2077	435	1930	2365
	Spec:90.1%	Spec:80.2%	Spec:100%	Spec:80.2%	
		NPV:87.8%		NPV:81.6%	

Table 3
The Hosmer-lemeshow goodness of fit test

Declie of Risk	Survival		Non-survival		Total
Hospitalmortality	Observed	Expected	Observed	Expected	
The Hosmer-lemeshow goodness of fit test of ApechII 3 day					
1	341	341.392	14	13.608	355
2	327	330.766	28	24.234	355
3	329	321.526	26	33.474	355
4	318	311.866	37	43.134	355
5	302	299.902	53	55.098	355
6	275	284.631	80	70.369	355
7	269	266.116	86	88.884	355
8	239	244.417	116	110.583	355
9	207	211.180	148	143.820	355
10	148	143.203	206	210.797	354
The Hosmer-lemeshow goodness of fit test of ApechII 1day					
1	565	581.870	65	48.130	630
2	562	561.981	68	68.019	630
3	563	548.176	65	81.824	630
4	534	535.885	96	94.115	630
5	542	524.260	88	105.740	630
6	519	512.451	111	117.549	630
7	517	499.186	113	130.814	630
8	488	483.031	142	146.969	630
9	426	458.489	204	171.511	630
10	382	394.670	251	238.330	633

The predictive value of dynamic APACHE II score for hospital mortality

Analysis of discrimination of APACHE II score on day 1,2,3,5,7,14 and 28 for predicting hospital mortality using ROC curves are shown in Fig. 2, The earliest time point when the achieved AUROC was greater than previous days was on day 3 ($P < 0.001$). (APACHE II 1: 0.579 [95%CI:0.516–0.642], APACHE II 2: 0.587

[95%CI:0.524–0.650], APACHE II 3: 0.666 [0.607–0.726], APACHE II 5: 0.695 [0.636–0.755], APACHE II 7: 0.701[0.643–0.759], APACHE II 14: 0.807 [0.759–0.854] and APACHE II 28: 0.934[0.909–0.959]).

Comparing the area under the ROC curve with the histogram, it is found that the area under the ROC curve on the third day is the earliest time point than the previous days to predict hospital mortality($P=0.024$) (Fig. 2b). To this end, Our subsequent analysis focuses on the development of APACHE II 3 as an optimal predictor of hospital mortality.

The third day Youden index was used to analyze the survival and non-survival group showed that in the APACHE II ≥ 17 group, 928(23.1%) patients were in the non-survival group, the sensitivity was 92.8%, PPV was 23.1%, 3081 patients (82.2%) were in the survival group, the sensitivity was 82.2%. In the group of APACHE II less than 17, 288 patients were non survival, the specificity was 90.1%, 2077 patients were survival, the specificity was 80.2%, NPV was 87.8% (Table.2). In the Kaplan-Meier survival curves, APACHE II less than 17 had higher survival rate($P=0.0001$)(Fig. 3).

The predictive value of dynamic APACHE II score for 90-day mortality

The APACHE II 3 day ROC curve for predicting 90-day mortality was 0.743(95% CI : 0.729–0.756, $P=0.001$), Youden index of 17 was used to analysis of 90 day survival status,indicated that in the group of APACHE II less than 17, 435 patients were non survival, the specificity was 100%, 1930 patients were survival, the specificity was 80.2%, NPV was 81.6%.(Table.2)

Score Calibration

The results of Hosmer-lemeshow goodness of fit test of APACHE II 3 day showed that there was no statistical difference between the predicted value and the actual value($X^2 = 6.198$, $P=0.625$), indicating that the model has a good predictive calibration ability(Table.3). The consistency of predicted death and actual death was 79.4%. For APACHE II on 1 day, the calibration is poor ($X^2 = 294.898$, $P<0.001$)(Table.3).

Discussion

This is the first article on the relationship between dynamic APACHE II score and outcomes of ICU patients, and found that APACHE II score on the third day was the optimal predictor of outcomes in ICU patients.

Many studies have confirmed that APACHE II score is a useful prognostic marker of mortality. A retrospective study of 200 Iranian patients admitted in ICU reported that an APACHE II score of 15 provides the best diagnostic accuracy to predict mortality of critically ill patients[6].Liu J have shown that initial APACHE II scores on day of ICU admission and correlated with survival outcomes[16]. A study included 109 cirrhotic MICU patients reported that APACHE II can be a predictor of mortality[17]. This help in categorizing patients and to facilitate early risk identification. These studies used APACHE II scores within 24 h after admission, although early identification of mortality helps to classify patients and early

identify risks. However, many factors affecting the prognosis of ICU patients within 24 h were ignored. This study founded that the APACHE II scores on the first day have poorly calibration on hospital mortality. This results is consistent with that of Kim[8], They founded that in the analysis of 826 Koreans patients, the APACHE II from the first 24 h after admission to the ICU exhibits poor calibration for hospital mortality. In large representative study of 141,106 ICU patients in the UK also confirmed that APACHE II showed good discrimination but imperfect calibration for hospital mortality[18]. Therefore, a new model is needed to accurately predict mortality in ICU patients. In recent years, although many new models have been developed to predict the mortality of ICU patients[19], these new models still need to be verified by multi-center and large sample studies. APACHE II score is still a high acceptance score, therefore, it is more meaningful and popular to find an effective score based on APACHE II score to predict outcomes of ICU patients.

Just as the accuracy of dynamic SOFA score in predicting sepsis is higher than that of SOFA score[7, 20, 21]. Some scholars suggest that the APACHE II score should be proposed during the initial 7 days of ICU stay to reduce the error to the greatest extent[22]. However, due to the complexity of APACHE II score, daily assessment will bring huge workload, so it is more valuable to find out the optimal time to predict outcome of ICU patients. In this study, Serial APACHE II scores were calculated on day 1, 2, 3, 5, 7, 14 and 28 after admission to ICU, and found that APACHE II scores on day 3 is a useful predictor of hospital and 90-day mortality in ICU patients.

Bahtouee' study have reported that APACHE II with a score of 15 gave the best diagnostic accuracy to predict ICU mortality[6]. In a study by Hosseini et al and Fadaizadeh et al reported the best cut-off point chosen was 13.5 in APACHE II score predicted hospital mortality, These result is lower than the 17 points we got in this study. This difference may be related to the following factors: First, Based on the date from the first 24 h after admission to ICU[23, 24]. There maybe ignore influenced factors as recent and ongoing resuscitation and therapy. Second, The sample size of the previous study is small, and this study uses a larger sample size, so we can draw a more reliable conclusion. Third, The 17 score of this study were obtained from the third day of APACHE II, while the previous study was the first, so different conclusions were drawn.

There are still limitations in this study. Firstly, this study is a retrospective study, but all the necessary data have been collected, so it limits the possible bias of this method. Second, all the date are from the MIMIC-III (2001–2012), the results may not reflect current practices, Besides, most of pateint included in MIMIC-III are from North American ICUs who descended from different populations. Third, our study only included date availavle online and more external validation is still required.

Conclusion

We explored the correlation between APACHE II score and outcomes of ICU patients, and found that APACHE II score on the third day was the optimal time to predict outcomes in ICU patients. These finding will help medical make clinical judgment and sound clinical sense.

Abbreviations

APACHE II

The Acute Physiology and Chronic Health Evaluation II; AUROC:Area under the receiver operating characteristic; SOFA:Sequential Organ Failure Assessment; SAPS:Simplified Acute Physiology Score; MIMIC:Medical Information Mart for Intensive Care; LOS:length of stay; ICD-9:International Classification of Diseases-9th

Declarations

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Author contributions

YT and YY contributed to the initial study concept and design. SYW obtained funding for the study. JZ, XD and HC contributes to the final study design. YT, YY and SYW participated in the first drafting of the manuscript. YT and YY perform data collectoin, and date analysis. KXC and XM contributed in comment on the manuscript and statistical analysis. All authors participated in the critical revision for intellectual content, and read and approved the fnal manuscript.

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Compliance with ethical standards

There are no conflicts of interest to disclose.

Ethical approval

The data of this study are from MIMIC-III database, and do not involve ethical approval.

Consent to participate

The data of this study are from MIMIC-III database, Consent to participate are not applicable.

Availability of data and materials

All data needed to evaluate the conclusions of this article are present and tabulated in the main text or in the ESM. For individual de-identified raw data that underlie the results reported in this article, please contact the corresponding author after publication.

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Figures

Fig.1

Figure 1

Flow chart. Illustration of exclusion and inclusion criteria as utilized to select the final patients.

a

b

Figure 2

APACHE II on follow-up days as predictor of hospital mortality. a Receiver operating characteristic(ROC) curves for the association of series APACHE II with hospital mortality. b Comparisons of AUROCs of APACHE II . p values are provided.

Figure 3

Survival rate in APACHE II >17 and APACHE II ≤17 groups.