ORIGINAL INVESTIGATION

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Evaluation of Basic Parameters for Prediction of ICU Mortality

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ABSTRACT

Aim: The performance of common mortality prediction models in the intensive care units (ICU) are extensively validated, predominantly in high-income countries. Simple and fast models with region specific features are needed.

Study design: Retrospective case-control study

Methods: We reviewed the medical records of 1057 ICU-admitted patients within three years. Patient survival was defined as discharge before 28 days. Multivariate logistic regression modeling was applied, basic parameters were selected, and a simple model was tried using four of them (age, albumin, platelet, C-reactive protein); as Quick Prediction of Mortality (Qpm) score, and then tested. The Qpm score predictions were compared to calculated *APACHE II predicted mortality* (APM) score predictions. Both scores were then weighted by calculated standardized mortality ratios (SMR).

Results: 933 patients were included into the analyses. The patients' overall observed mortality rate was 47%. APACHEII score prediction was 49% ($p< 0.001$, AUC= 0.810, r: 0.518). Qpm score prediction was 57% ($p< 0.001$, AUC= 0.699, r: 0.338). The SMR for Qpm was 0.82 in comparison to APM score SMR = 0.96.

Conclusion: This simple prediction model has showed an acceptable performance in our ICU sample and needs to be prospectively evaluated for feasibility. In addition, further studies could be planned for external evaluations and validations in different settings.

Key words: mortality prediction, critical care, scoring systems, platelet, albumin, CRP.

Introduction

Expanding technological advances served significant medical improvements and life expectancy increased globally, as world population continued to grow, with unprecedentedly aged population (1). Consequently, prevalence of age-related diseases and comorbid conditions requiring intensive care unit (ICU) increased. However, advanced technology and industrial systems introduced new health risks and diseases and transformed or modified like super resistant bugs, those all were increased burden of ICUs. Attainability of ICU beds that solely depends on economic and human resources has also grown at least for high-income countries (HICs), but for others, lower-income and lower middle-income countries (LICs) have great challenges due to economic disparities (2). Besides, UN-DESA reports that more than half of the world's population lives in low-income settings, and prospects 1 in 5 countries will economically decline in 2020 (1). In LICs, partly due to geopolitical reasons (disasters, both natural and manmade) and scarce resources, the burden of critical illness exceeds existing capacity. This burden comprises mainly of young population, in contrast with HICs where elders predominate. Critical care resources are limited and expensive, therefore appropriate utilization of ICU beds is essential especially in resource poor settings (RPS). Restricted or limited intensive care beds, infrastructure, personnel, and equipment are more challenging in RPS, where higher mortality rates has been reported because of not only limited resources but also those highest illness severity patients could attain critical care (2). Necessarily, maximizing the feasibility of scarce resources requires a great attention to regionalization and integration of local realities, population-based incidence, and prevalence. A feasible triage will improve the accessibility and quality of care, can thus potentially save many lives (2, 3).

List of prognostic models have been recommended and used to assess which patient would benefit the best (4). Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score (SAPS) are of common scales used in ICUs (5-7). Required parameters scale up to dozens, and typically based on the worst dip or peak values within the first 24 hours. On the other hand, some scores need periodic assessments. In consideration, most are complex in nature, time consuming, and resource utilizing and expensive, each has its own disadvantages (8). Vincent and Moreno described an ideal organ dysfunction score could be used in triage as; simple, inexpensive, routinely available in all ICUs, available at ICU admission, reproducible in several types of ICUs from different regions of the globe, and reliable and objective (4).

The performance of common models extensively validated, but predominantly in HICs. In RPS, used prognostic models are needed to be validated for relevant settings. These results may not be reproducible in RPS, because of not only different case-mix and regional specific characteristics but also missing predictor variables that are routinely available in HIC but are not obtainable or reliable in RPS (9). Those factors may influence the model performances, and then require adjustment in predictors, model revisions, and addition or removal of new predictors. An incomplete dataset confounds interpretation of prognostic model performance in RPS, thus, setting-adapted and simpler prognostic models are warranted (10).

In recent decades, disease scoring / diagnostic scales have been in a trend of shrinking to fewer components, in need of faster, simpler, feasible prediction criteria, preferably accurate as antecedents', especially in context of RPS (11-13). In these circumstances, who should benefit from critical care becomes not just an ethical consideration but also a matter of survival.

In this study we intended to evaluate basic admission parameters for simple prediction of patient mortality in our ICU sample, and then tried to build a simple and quick prognostic model using few predictors, to help and assist physicians in their decision-makings, to improve patient outcomes, and to provide cost-effectiveness.

Materials and Methods

Patient Population

This study was designed as a retrospective case-control cohort and conducted in a mixed-type (medical / surgical) 10-bed tertiary academic hospital ICU clinic. We reviewed medical records of 1057 patients who were admitted to ICU between January 1st 2013 and December 31st 2015. Hospital software (Enlil©, v.2.20, Mergen Tech, TR) system was used in data search and collections. A total of 933 patients were included into the analyses after exclusion of 124 patients because of age criteria (<18 and >90), pregnancy, re-admission, loss to follow-up to 28-day, no-consent, and missing data, (Figure 1).

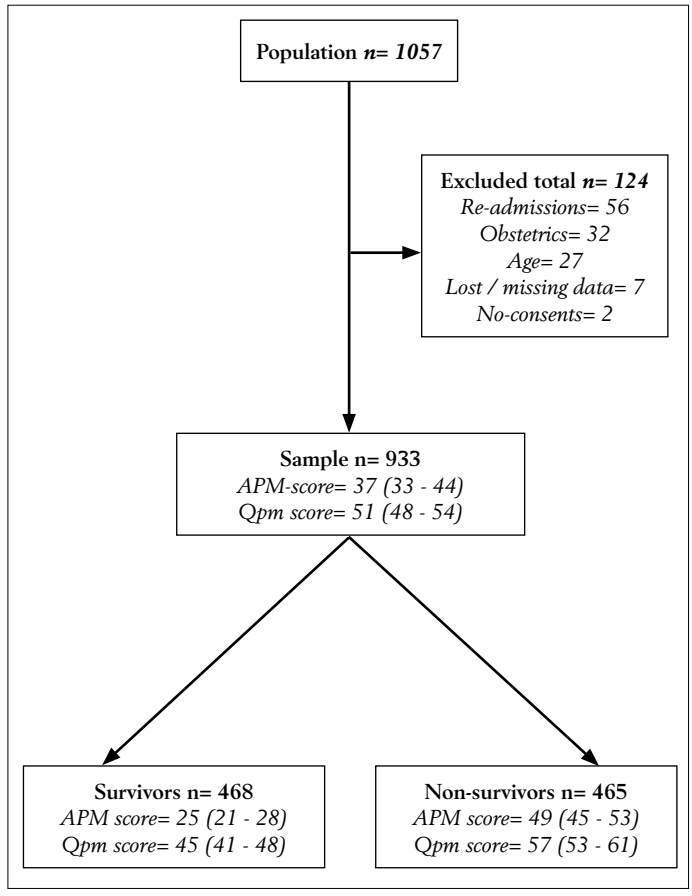

Figure 1. Patients selection diagram showing inclusion and exclusion process, survivors, and non-survivors (frequencies), APM and Qpm scores (mean and 95% confidence intervals).

APM-score; (adjusted) APACHE II (Acute Physiologic And Chronic Health Evaluation II) score predicted mortality score, Qpm-score; Quick prediction of mortality score.

Informed consents for "using medical records for scientific purposes and presentations (names disclosed)" had been asked and received from patients or legally authorized relatives. That is an institutional policy and instruction for every ICU admitted patient. The ethics approval was received from local review board.

Data collection and Definitions

Patients' age, gender, primary diagnosis, APACHE II scores and basic laboratory parameters at the admission were recorded. The primary out-come measure was all-cause ICU or in-hospital mortality within 28 days. Patients discharged before 28-day were accounted as survivors (n=468), the others as non-survivors (n=465). Group parameters were compared for relation to survival (Survivors vs. Non-survivors). Four basic parameters were selected and tested in this study for mortality prediction: age, albumin, platelet (PLT), C-reactive protein (CRP). The composed effect of these four parameters was assessed by multivariate logistic regression analyses (LRA) and a product equation was formed. Proceeding, this equation function was named as *Quick prediction of mortality* (Qpm) score. APACHE II predicted mortality (APM) score, adjusted for diagnoses, was also calculated. The standardized mortality ratio (SMR) was calculated as observed deaths / expected deaths for APM and Qpm, and then compared.

Statistical analysis

Variables were reported as frequencies and percentages, means and standard deviations, and confidence intervals (CI) when appropriate. The parameters were tested for normality. ANOVA, Chi-Square, Pearson's correlation tests were conducted to compare parametric and categorical variables when required. A statistical P value <0.05 was considered as significant with 95% CI.

Multivariate LRA were performed with all recorded admission parameters those were in patient medical record files, demographics, characteristics, complete blood counts, biochemical screens, arterial blood gas analyses, and physical examination findings. The model was progressed by forward regression adding candidate predictors for full main effects, with a cut-off value of P = 0.05.

Model calibration was assessed and evaluated using Lemeshow–Hosmer goodness-of-fit tests. Split sampling (random 50%) and bootstrapping (1,000 samples) methods were carried to test and provide more stable estimates. Model discrimination was assessed by receiver operating curve (ROC) analysis and Area Under the Curve (AUC) sensitivity / specificity values. The calculated best cut-off values were selected as *mean+1*SD* for both APM (26<) and Qpm (69<). Standardized mortality ratio calculations were processed as observed and predicted mortality ratios. The contingency table formed by drawing 2 × 2 matrices, accuracy, and effect size (Cohen's D) were calculated. The Qpm score internal performance reliability was tested (Cronbach's Alpha scale reliability).

All statistical analyses were conducted by SPSS© (SPSS© v20.0, IBM, IL, USA) software program. Missing values in predictors were calculated as less than 5% of all evaluated data. In order to avoid a selection or overfitting bias issues, those data were treated as if values were calculated mean of relevant parameter, assenting a lower power.

Results

After exclusions, 933 patients were included into analyses. General characteristics of patients are presented in Table 1. Multivariate LRA showed that age, PLT, CRP, and albumin levels significantly related to patient mortality. The prediction formula was constructed according to variables and coefficients in this multivariate LRA (Table 1).

The Qpm score was formulated as below:

$1 / (1 + \exp^{-(1.12354 + (0.01616 * age) - (0.00322*PLT) - (0.53455*Alb) + (0.02357*CRP))})$.

Observed patient mortality rate was 47%. The predicted mortality rate of Qpm score was 57% and APM score was 49%. Therefore, SMR (observed / predicted) for APM was calculated as 0.96 and it was 0.82 for Qpm (Table 1).

A LRA to test predictive relation of APM and Qpm scores with patient mortality was performed and both Qpm and APM scores showed statistical significance. Qpm score *t* and *B* values and *CIs* comparisons to APM was presented in Table 2.

The cut-off values were tested and evaluated in further prediction analyses. Cut-off values were determined by *t-test mean+1*SD*. Qpm cut-off value was calculated as 69 <, and 26< for APM. Pearson's analysis to evaluate correlation of defined cut-off values with mortality showed that both Qpm and APM scores were significantly correlated (Qpm p<0.001, r=0.338; APM p<0.001, r=0.518) (Table 3).

Table 1. Presentation of patient age, PLT, Alb and CRP levels (mean ± SD), APM and Qpm scores (mean and 95% CI), calculated SMR values, statistical differences between survivors and non-survivors, and β-values by multivariate logistic regression analysis.

	Survivors (n=468)	Non-survivors (n=465)	Total (n=933)	β	p	SMR
Gender						
Male	219 (54%)	190 (46%)	409			
Female	249 (48%)	275 (52%)	524			
Condition						
Medical	295 (41%)	426 (59%)	721			
Surgical	173 (82%)	39 (18%)	212			
LOS *(days)*	7.5 ± 0.5	8.5 ± 0.6				
LRA Intercept	-	-	-	-1.12354	-	
Age*(years)*	65 ± 18	70 ± 16	68 ± 17	0.01616	< 0.021	-
PLT *(K/uL)*	272 ± 137	200 ± 134	236 ± 140	0.00322	< 0.001	-
Alb *(gr/dl)*	3.3 ± 0.6	2.9 ± 0.7	3.1 ± 0.7	0.53455	< 0.001	-
CRP *(mg/dl)*	8.3 ± 9.5	13.4 ± 11.9	10.9 ± 11.1	0.02357	< 0.001	-
APM-score	25 (21 – 28)	49 (45 – 53)	37 (33 – 40)	-	< 0.001	*0.96*
Qpm-score	45 (41 – 48)	57 (53 – 61)	51 (48 – 54)	-	< 0.001	*0.82*

LRA: logistic regression analysis, **LOS:** length of stay, **PLT:** Platelet count, **Alb:** Plasma albumin level, **CRP:** Serum C-reactive protein level, **APM-score:** (adjusted) APACHE II score predicted mortality score, **Qpm-score:** Quick prediction of mortality score. **SMR:** standardized mortality rate (number of observed deaths / number of expected deaths), **CI:** confidence interval.

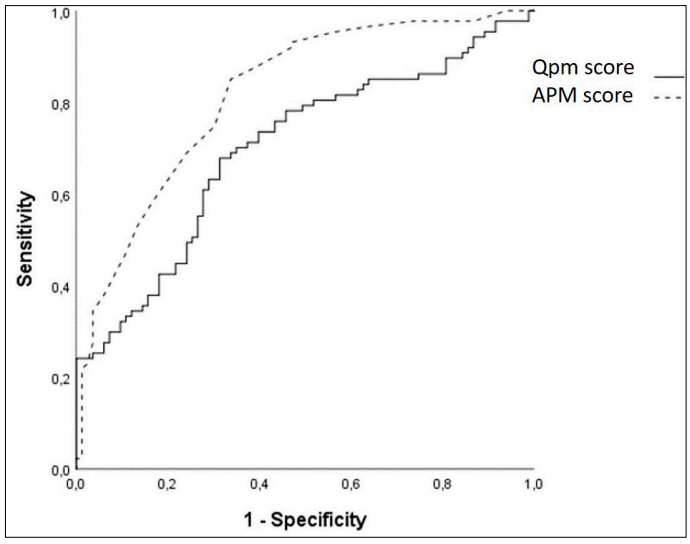

Figure 2. ROC curve predicting abilities of score parameters for 28-day mortality.

ROC: Receiver Operating Characteristics, **APM-score:** (adjusted) **APACHE II** (Acute Physiologic and Chronic Health Evaluation II) score predicted mortality score, **Qpm-score:** Quick prediction of mortality score.

The ROC curve analysis with defined cut-off values was also resulted with high statistical significance (Qpm p<0.001, AUC=0.699; APM p<0.001, AUC=0.810), as presented in Table 3 and Figure 2.

A *contingency* 2x2 table of observed vs predicted mortality rates based on predefined cut-off Qpm value (69<) was produced. Calculated specificity of Qpm was 92%, and sensitivity was 37%, with 4.65 likely-hood ratio (LR) and 6.78 odss ratio (OR), presented in Table 4.

Calculated accuracy was 65%, with 0.36 reliability (Cronbach's alpha). Goodness of fit test (Hosmer and Lemeshow) resulted that chi^2 =18 with p=0.02.

Discussion

The health care delivery pattern in RPS might be markedly different from HICs. Critically ill patients managed in nursing homes, government, and private hospitals, even in wards before an ICU bed available, can partly explain the high mortality rates in patients with relatively lower calculated probability of death. Because of shortage of ICU beds, a triage is often performed to select patients for ICU admission, with preference given to younger patients and those with clearly reversible illnesses. This alone can also account for differences in observed mortality versus predicted risks. An important factor usually implicated in the poor performance of severity scoring systems in the developing world is the different pattern and a relatively poorer quality of medical and nursing care delivered in these ICUs. Because a model theoretically performs best in a population with a similar case-mix as the population from which the model was derived, such a model is unlikely to fit well in this new population.

Table 2.: Predictive relation analysis of APM and Qpm scores with observed 28-day patient mortality.

	t	p	β	CI 95%	
APM-score	8.9	< 0.001	1.1	0.854	1.342
Qpm-score	4.7	< 0.001	0.93	0.536	1.326

APM-score: (adjusted) **APACHE II** (Acute Physiologic and Chronic Health Evaluation II) score predicted mortality score, **Qpm-score:** Quick prediction of mortality score.

Table 3. Pearson's and ROC analyses results presenting correlation and predictive ability of APM (26<) and Qpm (69<) scores with observed 28-day mortality.

	Pearsons correlation analysis		ROC analysis		
	p	r	AUC	95% CI	*p*
APM-score	< 0.001	0.518	0.810	0.753 - 0.867	< 0.001
Qpm-score	< 0.001	0.338	0.699	0.620 - 0.777	< 0.001

ROC: Receiver Operating Characteristics, **APM-score:** (adjusted) **APACHE II** (Acute Physiologic And Chronic Health Evaluation II) score predicted mortality score, **Qpm-score:** Quick prediction of mortality score, **AUC**: Area Under Curve, **CI:** confidence interval.

Table 4. The 2x2 contingency table of Qpm score for relation to observed patient mortality.

	Survivors *(n)*	Non-survivors *(n)*		
Qpm <69	431	294	Sensitivity= 37% CER= 0.41 LR= 4.65	*Specificity= 92%* *EER= 0.82* *OR= 6.78*
Qpm >69	37	171		

Qpm-score: Quick prediction of mortality score, **OR:** odds- ratio, **EER:** experiment event rate, **CER:** control event rate, **LR:** likely-hood ratio.

In the present study, we suggested a new simple prognostic model for mortality risk assessment of ICU patients. We propose that a prediction model usually represents its specific population and settings, and its generalizability is a challenging issue. For example, Evran et al. conducted a study in Turkey as our study was, that compared scoring systems. (14). They reported a lower mortality rate than we did. This is possibly due to post-operative and surgical patients constituted the majority of their sample. That is the point *case-mix* matters in terms of model prediction ability. Considering that ICU samples were confounded by various factors, including local admission practices, area specific and endemic conditions, etc., predictive ability of a model would be unreliable even in same local circumstances. Generalizability of a prediction model usually required large data sets; to fit in different situations, patient populations and time intervals, internally and externally validated, recalibrated if necessary, and preferably compared with multiple existing models.

In our study, we produced a simple LRA model constituted by the composed effect of age, PLT, Alb and CRP parameters for mortality prediction, formulated and postulated a Qpm score, compared with APM score. Qpm score showed significant difference between survivors and non-survivors and had a discriminative ability. APM score ability was better than Qpm, but Qpm calculation was fast and simple. When cut-off values were included Qpm score has gained a better performance. Thereby, it could be proposed to use

Qpm score by that cut-off value to assess higher or lower risk of mortality. Hence, as shown in contingency table calculations, Qpm score with the cut-off value was presented a 37% sensitivity, 92% specificity, 4.65 likely-hood ratio and 6.78 odds-ratio. This was supported by a ROC curve analysis.

On the other hand, these results should be predicted cautiously due to retrospective nature of the study. the repeatability and generalizability of these results should be tested prospectively, for similar and also for different cohorts. These reported values of our study could be assessed as over-predicting effect. In a Bangladeshi and an Indian study, this affect was described in comparison of APACHE II and SAPS II performance, both were poor in Hosmer-Lemeshow test, but good in discrimination by ROC analyses similar to our study (15, 16). A different north Indian study on classic models showed modest discrimination and poor calibration, otherwise, underpredicted the mortality in patients with lower probabilities (17). These study results were explainable by regional differences and smaller sample sizes, as we had. In order to over-come this issue, some studies purposed a sequential scaling could be more producible than a single score calculation (18, 19). In our study, we mostly focused on a single admission data assessment for feasibility.

In contrast to our model, a Greece study collected twelve variables during the first ICU day that were used to develop the new prediction model, demonstrated better performance (discrimination and calibration) and predictive ability in local patient population than the APACHE II, SAPS III and SOFA scoring systems (20). In a Rwanda study, five clinical variables: age, suspected or confirmed infection, hypotension or shock, Glasgow Coma Scale (GCS) score, and heart rate at ICU admission also showed a good discrimination (21). In a South Asian model based on available resources included simple variables showed good performance (22). These finding are supportive of that simple models are also capable of discrimination in RPS.

Besides these basic models, an Indian study on sepsis mortality prediction combined SAPS II, SAPS III, and SOFA scores that was useful and prognostic, but was a complex procedure (23). Indian and Iranian studies found no statistically significant difference in efficacy and performance of classical models (24, 25). In addition to this, two studies from Pakistan and also one from Nepal favored APACHE IV system, but that required too many variables to obtain in RPS (26-28). The MEXSOFA study, using the original SOFA with two modifications, by a simpler method, showed good performance (29). Philippines study found SAPS prediction model showed fair discrimination and but a good calibration in predicting mortality (30). In a large sample Australian study, they compared an administrative-only and a clinical model that clinical model showed a better performance and adding APACHE scores to the administrative model was not better than clinical model (11). In a Brazilian study, all models showed poor calibration, while discrimination was very good for all of them (31). Previously mentioned studies in RPS had poor calibration but good discrimination, as in our study.

Poor performance of a model in new patients may be explained by inadequate model derivation, overfitting, or omission of important predictors, in turn would affect generalizability to remain stable when applied to cohorts from different time periods, different patients. But it should be mentioned that the choice of scoring system should be considered at respect of the ease of use in local preferences.

ICU profiles vary greatly worldwide, depending on the proportion of case-mix, triage, admission, and discharge policies, availability of beds and staffing. Therefore, external validation performance of a severity score, also referred as generalizability or transportability, requires some attention to regional variabilities. The apparent performance of a model is often optimistic, that the model was designed to optimally fit its original derivation data set, as in our study. Thus, large-numbered data sets were advised to overcome this issue. Not to forget that, non-significance does not always mean absence of evidence, especially for studies with a limited sample size, and vise-versa.

Limitations

The main limitation of this study was that an external validation was lacking. In addition to this, a perfect calibration could not have been gained, and over-fitting or stability issues were not excluded. In order to provide more stable estimates Qpm score was processed by split sampling and bootstrapping. The Cronbach's Alpha scale reliability was not satisfying (0.356) indeed, but 70% Cohen's D effect size was relatively acceptable. Pearson's correlations resulted with significant p but with low r estimates for Qpm. However, it was advised that some care must be exercised in the interpretation of this calibration tests as that were dependent on sample size. Thus, a better significance could be achieved with increasing sample size. Mention that predictive accuracy of severity scoring systems in RPS ICUs does not fit well owing to differences in HICs. More studies in multiple centers involving larger patient population are needed to validate new scoring systems in RPS for good predictability, as our proposed model.

Conclusion

This simple prediction model has showed an acceptable performance in our ICU sample and needed to be prospectively evaluated for feasibility. In addition, further studies could be planned for external evaluations and validations in different settings.

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All contributors of this study do meet the criteria of authorship.

AUTHOR CONTRIBUTIONS:

Concept: NT, VI; **Design:** NT, VI; **Supervision:** NT, VI; **Fundings:** NT, VI; **Materials:** NT, VI; **Data Collection and/or Processing:** NT, VI; **Analysis and/or Interpretation**: NT, VI; **Literature Search:** NT, VI; **Writing Manuscript**: NT, VI; **Critical Review:** NT, VI.

Ethics Committee Approval: Trakya University Medical Faculty Ethical Board, 2017/13, 02/03, 18 January 2017.

Informed Consent: Patients or legaly authorised kins

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Conflict of Interest: Authors have no conflicts of interest to declare.

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