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Categorical Apache IV prediction of ICU and 90 day mortality

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Abstract: The APACHE IV score is used to predict hospital mortality and for case-mix adjustments in benchmarking initiatives in critically ill patients. The timing of the evaluation of survival may be critical. Hence we evaluated categorical APACHE IV predictive scoring on ICU and 90 day mortality.

In a single center retrospective analysis all patients, admitted to the ICU of ZOL-Genk, Belgium, from 01-01-2019 to 01-01-2020 were included into the analysis. Data were verified by a single, trained medical doctor, who was blinded to the patient outcome. Mortality data were retrieved from the national death register. The subgroups were defined by their proper APACHE diagnostic category. Quantitative analysis of ICU and 90 day mortality by logistic regression based on APACHE IV predictions per diagnostic category and the 10 most important features responsible for ICU and 90 day mortality.

Over the 1 year period 2816 ICU admitted patients were included in the analyses. The mean age was 62.66 ± 16.94 years. The patients could mainly be classified into cardiovascular (34.10%), neurologic (25.58%) and respiratory (11.83%).

Mean APACHE IV scores were 55.73 ± 23.21 and the overall APACHE mortality prediction was 13.86% ± 18.26. The mortality rate during ICU admission and after 90 day respectively was 5.11% and 10.90%. APACHE mortality prediction on the total population and Apache IV categories relative to the recorded ICU and 90 day mortality demonstrated a considerable overlap. The percentage of post-ICU mortality (<90 day post ICU admission) relative to ICU mortality for each Apache category was notable. Every cohort studied (total population, categorical data) revealed other weights to the 10 most important features responsible for ICU and 90 day mortality.

In conclusion the APACHE IV score underestimates the 90 day mortality for a mixed ICU population. This was the case for all diagnostic subgroups. This difference could possibly be explained by the relative weights of the ten most important variables in the patients APACHE IV score.

Keywords: Critical illness; prediction; mortality; ICU; Acute Physiology and Chronic Health Evaluation.

Introduction

Severity scores in critically ill patients are used for estimations of in hospital mortality and for case-mix adjustments in benchmarking and clinical studies. The most commonly used ICU severity scores are the Acute Physiology and Chronic Health Evaluation (APACHE) score, the Simplified Acute Physiology Score (SAPS) and the Mortality Probability Model score (MPM) (1-3). These models have not only been updated over the years, but also validated in different countries, healthcare systems and patient populations (4). Making sure that the models are "fit" for a general ICU population or specific subgroups such as cardiac, neurological and septic patients is the most important challenge. For entire patient populations these models often have a generally good discrimination. However, calibration

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and prediction of mortality at individual patient level are not surprisingly much more problematic.

APACHE IV (Acute Physiology And Chronic Health Evaluation) score, initially published in 2006 (5) is the latest version of the APACHE-II score, published in 1985 (6). The score is calculated based on 129 variables derived within the first 24 hours of the ICU admission. The score has been developed in ICU's in the USA.

It has demonstrated its value in predicting outcomes based on severity of illness and pre-existing patient characteristics (7). APACHE scores are probably the most widely used in intensive care and provide the basis for the calculation of an estimated risk of death in hospital and estimation of the length of stay. Although ICU mortality reflects the result of severity of illness relative to the care provided on ICU, the discharge criteria from ICU vary widely across the world. In hospital or ICU mortality are usually calculated for the index stay. The index stay is the stay in the hospital, which the patient was initially admitted to. Hence, patients who die after referral to another hospital are not counted as non-survivors. Therefore, in clinical trials and benchmarking initiatives we are evolving towards long-term landmark mortality outcome. While in the past ICU and 30 day survival were the standard mortality measures, the 90 day and 180 day survival rates are now the gold standard (8). 90 day mortality probably better indicates the attributable mortality from an episode of critical illness.

In this study we aimed to analyze the difference in discrimination of the APACHE IV score for ICU mortality versus 90 day mortality in a single center setting of a mixed ICU. At the same time we quantitatively analyzed ICU and 90 day mortality by logistic regression based on APACHE IV predictions per diagnostic category and provide the 10 most important features responsible for ICU and 90 day mortality.

Methodology

Patient population

This research was approved by the ZOL clinical trial unit and independent ethics committee. Since this is a retrospective analysis informed consent was waived. Adult patients (>17 years of age), admitted to the intensive care unit of Ziekenhuis Oost-Limburg, Genk, Belgium, a tertiary, teaching, non-university hospital, in the period from 01-01-2019 to 01-01-2020 were included into the analysis. The ICU of ZOL-Genk comprises 38 monitored beds, in which patients can be mechanically ventilated. There is no step-down unit for critically ill patients. All patients were included, also the ones that stayed for less than 24 hours.

Data collection

An automated APACHE IV calculator was built into the electronic medical record system of ZOL-Genk (HiX, ChipSoft B.V. Amsterdam, The Netherlands). This calculator was selecting the highest and lowest values of the variables from the electronic medical records of the patients, needed to calculate the APACHE IV score. The admission diagnosis and comorbidities were taken from the patient's admission template. Data were verified by a single, trained medical doctor (TB), who was blinded to the patient outcome (ICU and 90 day mortality). This was done to reduce the inter-operator variability and to avoid bias in the APACHE scoring when the outcome is known to the scorer. Mortality data were retrieved from the national death register. The subgroups were defined by their proper APACHE diagnostic category.

Statistical analyses

Data were analyzed using JMP 15.0.0 (SAS Institute, Cary, NC, USA) and Google Colab. Code of analysis is available at: https://github.com/SvenVanPoucke/Back-prediction/blob/master/ApacheIV.ipynb.

We calculated ICU and 90 day mortality by logistic regression based on APACHE IV predictions per diagnostic category and provided the 10 most important features responsible for ICU and 90 day mortality.

Results

General description

Over the 1 year period 2816 ICU admitted patients were included in the analyses. The mean age was 62.66 ± 16.94 years. The patients could be classified into cardiovascular (34.10%), neurologic (25.58%), respiratory (11.83%), gastrointestinal (10.87%), trauma (6.57%), musculoskeletal/skin (5.86%), metabolic (2.55%), genito-urinary (1.81%), hematological (0.60%) and transplant (0.18%).

Mean APACHE IV scores were 55.73 ± 23.21 and the overall APACHE mortality prediction was 13.86% ± 18.26 (min 0.10%; max 97.90%). The

mortality rate during ICU admission and after 90 day respectively was 5.11% and 10.90%.

Descriptive statistics of the survivors and non-survivors

The patient characteristics of the study population are described in Table 1. The entire study population has 2816 patients (Table 1A). In Table 1B the patients deceased during ICU stay (n=144) are described, while Table 1C is presenting the patients deceased within 90 day after ICU admission(n=308)

Table 1.A

Entire Population (n=2816)

Parameter	Average	Deviation
Minimal Alveolar–arterial gradient (mmHg)	109.36	104.15
Age (years)	62.66	16.94
Maximum Albumin concentration (g/L)	32.20	6.07
Minimum Albumin Concentration (h/L)	31.33	6.11
Maximum Bilirubin Concentration (mg/dL)	0.83	1.26
Maximum Creatinine Concentration (mg/dL)	1.88	8.19
Minimum Creatinine Concentration (mg/dL)	1.00	0.87
EMV (Eye, Motor, Verbal Glasgow Coma Scale)	14.10	2.59
Maximum Fraction Inspired Oxygen (%)	56.96	264.91
Maximum Glucose Concentration (mg/dL)	189.38	62.19
Minimum Glucose Concentration (mg/dL)	111.57	24.34
Maximum Heart Rate (beats/min)	98.21	20.62
Minimum Heart Rate (beats/min)	63.75	13.65
Maximum hematocrit (%)	36.55	5.99
Minimum hematocrit (%)	33.01	6.27
Maximum Mean Blood Pressure (mmHg)	107.71	24.70
Minimum Mean Blood Pressure (mmHg)	64.48	14.05
Maximum Arterial $C0_2$ Concentration (mmHg)	45.10	10.06
Minimum Arterial $C0_2$ Concentration (mmHg)	35.59	6.34
Minimum PaO_2/FiO_2 ratio	275.86	99.75
Minimum PaO_2 (mmHg)	73.73	19.14
Maximum pH	7.44	0.06
Minimum pH	7.34	0.08
Pre-ICU length of stay (day)	2.45	12.20
Prediction (Apache, %)	13.86	18.26
Maximum Respiratory Rate (breaths/min)	24.13	5.45
Minimum Respiratory Rate (breaths/min)	11.07	4.21
Score Apache	55.73	23.21
Maximum Sodium Concentration (mEq/L)	141.20	4.18
Minimum Sodium Concentration (mEq/L)	134.94	13.19
Maximum Body Temperature (°C)	37.49	0.71
Minimum Body Temperature (°C)	35.91	0.70
Maximum Urea Concentration (mg/dL)	45.08	35.22
Urine (litres/24u)	1.81	1.00
Maximum White Blood Cell Count (10^9/L)	13.75	6.52
Minimum White Blood Cell Count (10^9/L)	10.00	4.76

Post-ICU mortality by the diagnostic subcategories

90 day mortality (10.90%) was 113% higher than ICU mortality (5.11%). Post ICU mortality presented as the % of patients deceased after ICU discharge but before 90 day as % of total mortality per category was 42.42%, 65.79%, 50.00%, 33.33%, 91.67%, 50.0%, 63.33%, 52.38%, 100.0%, 38.10% respectively for cardiovascular, gastrointestinal, genito-urinary, hematological, metabolic, musculo-

Table 1.B

Deceased during ICU admission (n=144)

Parameter	ICU Mortality	
	Average	Deviation
Minimal Alveolar–arterial gradient (mmHg)	215.58	177.31
Age (years)	71.60	11.68
Maximum Albumin concentration (g/L)	29.75	6.76
Minimum Albumin Concentration (h/L)	28.53	7.09
Maximum Bilirubin Concentration (mg/dL)	1.15	1.35
Maximum Creatinine Concentration (mg/dL)	2.09	3.24
Minimum Creatinine Concentration (mg/dL)	1.51	1.03
Maximum Fraction Inspired Oxygen (%)	53.12	25.54
Maximum Glucose Concentration (mg/dL)	212.39	69.09
Minimum Glucose Concentration (mg/dL)	112.04	39.96
Maximum Heart Rate (beats/min)	109.21	23.81
Minimum Heart Rate (beats/min)	67.39	19.23
Maximum hematocrit (%)	35.50	6.69
Minimum hematocrit (%)	31.22	7.33
Maximum Mean Blood Pressure (mmHg)	108.91	29.68
Minimum Mean Blood Pressure (mmHg)	54.03	14.44
Maximum Arterial $C0_2$ Concentration (mmHg)	47.10	14.50
Minimum Arterial $C0_2$ Concentration (mmHg)	33.55	8.51
Minimum PaO_2/FiO_2 ratio	208.89	114.76
Minimum PaO_2 (mmHg)	73.85	39.86
Maximum pH	7.42	0.09
Minimum pH	7.28	0.13
Pre-ICU length of stay (day)	3.17	8.27
Maximum Respiratory Rate (breaths/min)	26.01	7.14
Minimum Respiratory Rate (breaths/min)	11.83	5.56
Maximum Sodium Concentration (mEq/L)	142.42	5.51
Minimum Sodium Concentration (mEq/L)	136.13	4.80
Maximum Body Temperature (°C)	37.36	1.20
Minimum Body Temperature (°C)	35.27	1.33
Maximum Urea Concentration (mg/dL)	76.10	49.90
Urine (litres/24u)	1.33	1.08
Maximum White Blood Cell Count (10^9/L)	14.42	9.10
Minimum White Blood Cell Count (10^9/L)	10.70	7.98

Table 1.C

Deceased within 90 day (n=308)

Parameter	90 day Mortality	
	Average	Deviation
Minimal Alveolar–arterial gradient (mmHg)	160.40	148.21
Age (years)	72.76	11.32
Maximum Albumin concentration (g/L)	30.19	6.00
Minimum Albumin Concentration (h/L)	28.95	6.37
Maximum Bilirubin Concentration (mg/dL)	1.09	1.69
Maximum Creatinine Concentration (mg/dL)	2.78	12.87
Minimum Creatinine Concentration (mg/dL)	1.41	1.19
Maximum Fraction Inspired Oxygen (%)	44.74	22.21
Maximum Glucose Concentration (mg/dL)	211.20	77.26
Minimum Glucose Concentration (mg/dL)	105.55	33.72
Maximum Heart Rate (beats/min)	106.96	23.54
Minimum Heart Rate (beats/min)	67.04	16.63
Maximum hematocrit (%)	34.80	6.69
Minimum hematocrit (%)	30.94	6.86
Maximum Mean Blood Pressure (mmHg)	108.00	27.75
Minimum Mean Blood Pressure (mmHg)	56.82	15.07
Maximum Arterial $C0_2$ Concentration (mmHg)	47.14	10.06
Minimum Arterial $C0_2$ Concentration (mmHg)	34.38	8.17
Minimum PaO_2/FiO_2 ratio	238.75	110.73
Minimum PaO_2 (mmHg)	71.75	30.34
Maximum pH	7.43	0.08
Minimum pH	7.30	0.12
Pre-ICU length of stay (day)	4.20	9.27
Maximum Respiratory Rate (breaths/min)	26.43	6.98
Minimum Respiratory Rate (breaths/min)	11.77	4.93
Maximum Sodium Concentration (mEq/L)	141.45	5.34
Minimum Sodium Concentration (mEq/L)	134.48	12.52
Maximum Body Temperature (°C)	37.42	1.00
Minimum Body Temperature (°C)	35.27	1.10
Maximum Urea Concentration (mg/dL)	71.66	49.04
Urine (litres/24u)	1.38	0.97
Maximum White Blood Cell Count (10^9/L)	14.36	8.30
Minimum White Blood Cell Count (10^9/L)	10.58	6.73

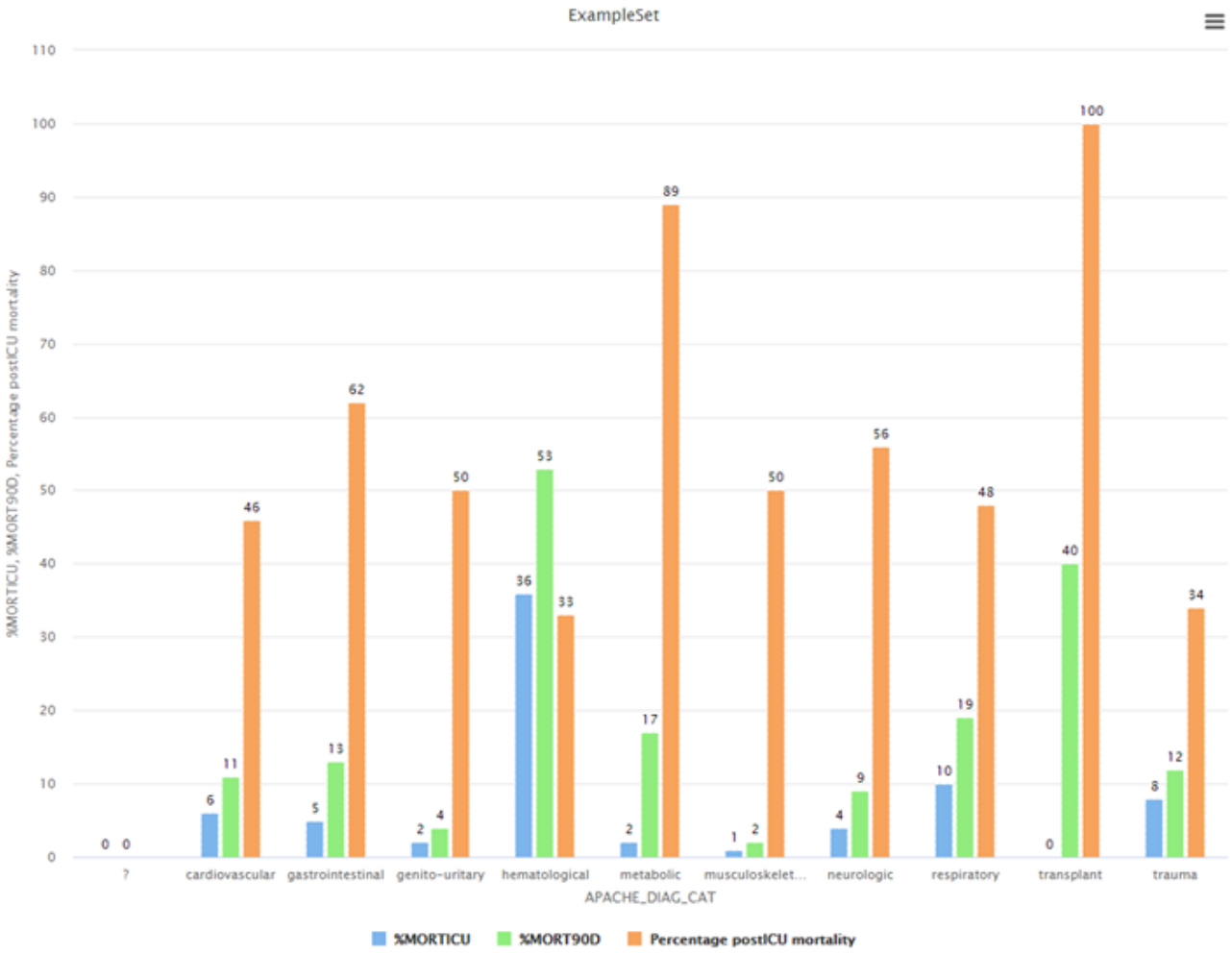

Fig. 1 — Percentage ICU (%MORTICU) and 90 day mortality (%MORT90D) with % post-ICU mortality relative to ICU mortality per Apache category.

skeletal/skin, neurologic, respiratory, transplant and trauma patients (Fig. 1).

Discrimination of 90 day mortality by the APACHE IV score

Figure 2 is a visual representation of the patients who had higher APACHE scores and thus a higher likelihood of dying and the actual survival. Each dot represents a single patient. The patients who died (red dots) are mainly situated in the right upper quadrant, while the surviving patients are in the lower left quadrant. However, there is an important overlap between the two subgroups. In the ideal setting the survivors and non-survivors are in completely separated clouds.

The performance of the APACHE IV score to predict ICU and 90 day mortality was analyzed for the entire patient population and the different diagnostic subgroups (Table 2). Prediction was further calculated by logistic regression on ICU and 90 day mortality. Results were represented as accuracy, classification error, AUC (area under the curve), precision, recall, f-measure, sensitivity and specificity.

Weight of APACHE IV variables in mortality prediction

In Table 3 the 10 most important variables to contribute to the ICU and 90 day mortality are described for the entire study population and the cardiovascular diagnostic subgroup. In the entire population the 3 most important variables are all related to the Glasgow Coma Scale, reflecting the neurologic state of the patient on ICU admission. In the cardiovascular subgroup minimum temperature, minimum PH and maximum urea levels are the strongest predictors of ICU mortality. There is only a minor difference in the top 10 variables between ICU and 90 day mortality. This accounted for all diagnostic subgroups.

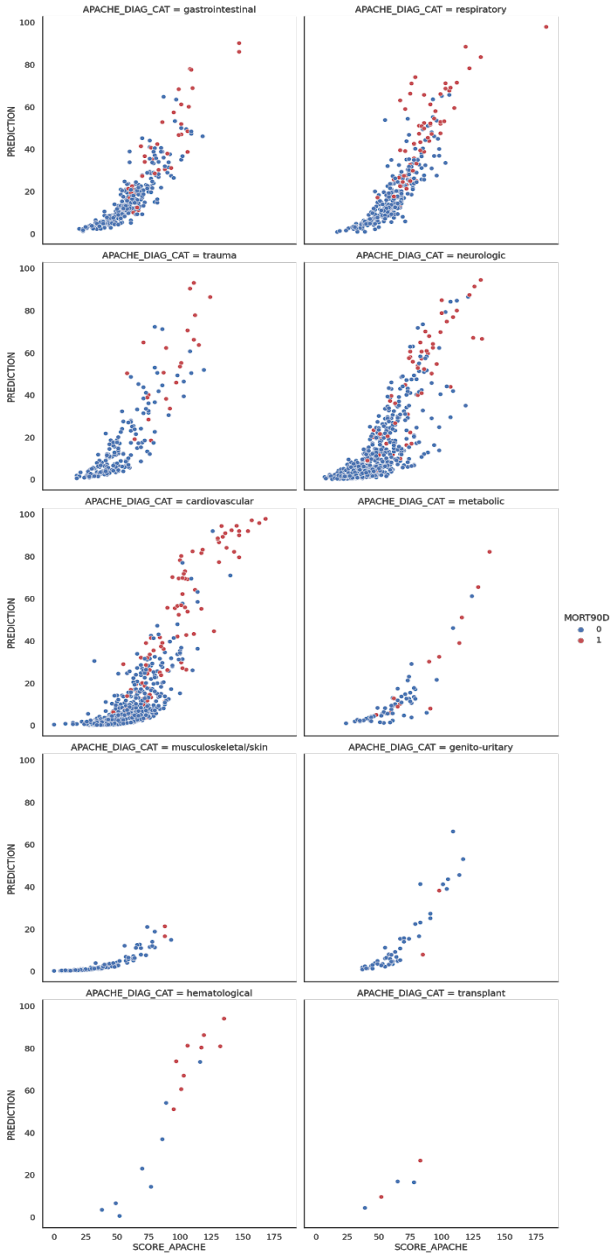

Fig. 2. — Prediction and Apache scores per category labeled for 90 day mortality (blue= survival, red= deceased).

Discussion

The APACHE mortality prediction on the total population (n=2816) relative to the recorded 90 day mortality demonstrated a considerable overlap, which is reassuring. However, we were surprised that the percentage of post-ICU mortality, within 90 days after ICU admission, was so high relative to ICU mortality. For the entire patient population the 5% ICU mortality increased to about 10%. This was the case for basically all APACHE diagnostic subgroups.

This observation might be related to the natural course of the disease and the quality of care during and after ICU stay. Our incentives to increase follow up of ICU discharged patients received quite some attention in our hospital and might in the future clarify at which point during and after ICU stay we might increase overall survival taking into consideration quality of life. Additionally, baseline functional status prior to critical illness as a strong independent predictor of mortality might receive more attention in the future (7).

ICU mortality is a simple endpoint that is easily available in hospital databases. It is useful in combination with an overall quality program (8) (9). Variation over time may reflect institutional and organizational events or characteristics, budget cuts, bed capacity pressure, and may be able to detect true quality deficiencies. Nevertheless, the correlation between quality of care and mortality is poor for some diagnoses and risk models for example Euroscore for CABG, APACHE SMR (10, 11). However, the definition of ICU is very hospital specific which can influence mortality (e.g. non-ICU step-down areas in some hospitals). As a consequence ICU mortality can be ‘gamed’ e.g. transfers out to die in the ward or other units. Hence it is cumbersome to use ICU mortality for benchmarking between hospitals.

Hospital mortality is a reasonable surrogate for 90 day mortality which is considered the gold standard. Hospital mortality compared to ICU mortality, avoids many problems of censoring at ICU discharge. As such, it gets over differences in definition of ICU and ICU discharge thresholds. Hospital mortality is still a simple and robust endpoint which is easy to obtain from existing hospital databases. Hospital mortality can confound intensive care outcomes with deficiencies in ward or other post ICU care. It does not address in any way functional outcomes.

90 day mortality is a simple robust endpoint which addresses the issue of ongoing mortality after hospital discharge. Most frequently the data is available by linkage with external registries (e.g. births, deaths and marriages). However, 90 day mortality is still an arbitrary time point, as is landmark 28 day mortality. However, the latter is also clearly inadequate since it too short term. 90 day mortality may still be insufficient to accurately measure the attributable mortality and functional outcome from an episode of critical illness. The downside is that 90 day mortality might be associated with problems of loss to follow up after ICU and hospital discharge. There may also be ethical implications of contacting patients after discharge (especially for research studies). Depending on disease it may

Table 2

		ICU Mortality		90 day Mortality	
Population/Category	Metric	Value	SD	Value	SD
Total	accuracy	0.96	0.02	0.92	0.01
	classification_error	0.04	0.02	0.08	0.01
	AUC	0.93	0.04	0.88	0.03
	precision	0.81	0.27	0.71	0.1
	recall	0.23	0.06	0.48	0.08
	f_measure	0.34	0.08	0.56	0.04
	sensitivity	0.23	0.06	0.48	0.08
	specificity	0.99	0.01	0.97	0.01
Cardiovascular	accuracy	0.96	0.01	0.92	0.02
	classification_error	0.04	0.01	0.07	0.02
	AUC	0.98	0.01	0.91	0.05
	precision	0.73	0.28	0.84	0.15
	recall	0.58	0.28	0.38	0.13
	f_measure	0.56	0.11	0.5	0.13
	sensitivity	0.58	0.28	0.38	0.13
	specificity	0.98	0.02	0.98	0.01
Neurologic	accuracy	0.96	0.02	0.93	0.01
	classification_error	0.03	0.02	0.06	0.01
	AUC	0.88	0.13	0.81	0.1
	precision	NaN	NaN	0.8	0.27
	recall	0.2	0.44	0.38	0.15
	f_measure	NaN	NaN	0.48	0.15
	sensitivity	0.2	0.44	0.38	0.15
	specificity	0.98	0.01	0.98	0.01
Respiratory	accuracy	0.91	0.04	0.85	0.04
	classification error	0.08	0.04	0.14	0.04
	AUC	0.17	0.17	0.91	0.09
	precision	NaN	NaN	0.57	0.07
	recall	0	0	0.72	0.28
	f_measure	NaN	NaN	0.61	0.13
	sensitivity	0	0	0.72	0.28
	specificity	1	0	0.88	0.05

reflect more the natural history of the disease rather than the ICU care per se.

Conclusion

Apache mortality prediction on the total population and Apache IV categories relative to the recorded ICU and 90 day mortality demonstrated a considerable overlap. The percentage of post-ICU mortality (<90 days post ICU admission) relative to ICU mortality for each Apache category was notable. Every cohort studied (total population, categorical data) revealed other weights to the 10 most important features responsible for ICU and 90 day mortality.

Table 3

	Entire population			Cardiovascular	
	ICU	**90 day**		**ICU**	**90 day**
Variable			**Variable**		
Verbal low	0.328	0.353	Temp min	0.317	0.270
EMV	0.326	0.373	PH min	0.290	0.242
Eye low	0.289	0.339	Urea max	0.254	0.331
Urea max	0.267	0.204	AaDO2 min	0.217	0.151
Age	0.209	-	Heart rate max	0.189	0.224
Temp min	0.194	0.211	BP min	0.177	0.180
BP min	0.191	0.173	Creat min	0.170	0.224
Creat min	0.168	0.134	Urine	0.163	0.206
Urine	0.152	-	PH max	0.150	-
Heart rate max	0.149	0.124	Glucose max	0.146	0.153
AaDO2 min	-	0.162	No CABG	-	0.153
PH min	-	0.178			

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