Sequential evaluation of prognostic models in the early diagnosis of acute kidney injury in the intensive care unit

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General and specific severity scores for patients with acute kidney injury have significant limitations due in part to the diversity of methods that have been used. Here we prospectively validated five general (APACHE II, SAPS II, SOFA, LODS, and OSF) and three specific (SHARF, Liaño, and Mehta) scoring systems in 366 critically ill patients who developed acute kidney injury in the intensive care unit. Sequential scores in each system were determined on the day that acute kidney injury was diagnosed, on the day when acute kidney injury–specific score criteria were achieved, and on the day of initial nephrology consultation. Acute kidney injury, defined as an increase of 50% or more in the baseline serum creatinine, was mainly due to sepsis, and had an incidence of 19% and an overall 68% mortality. A progressive improvement in score performance was found. On the day of initial nephrology consultation, most scores showed a good performance and two indices (SAPS II and SHARF) achieved an area under the receiver operating characteristic curve above 0.80. Calibration was good on all three defining days, except for OSF when score criteria were achieved, and Mehta at the time of nephrology consultation. Our study shows that early and sequential evaluation is a better approach for prognostic scoring in critically ill patients who develop acute kidney injury.

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Both general and specific scores have been applied to acute kidney injury (AKI) patients, particularly in the intensive care unit (ICU). The main objectives are to provide survival prediction and an accurate stratification of the severity of patients' illness for clinical studies, and evaluation of therapeutic interventions.[1] Currently, there are no universal, validated, and accepted scoring systems for AKI patients.[2] Studies have presented conflicting results due to difficulties such as variations in AKI definitions and the use of heterogeneous populations with different mortality rates, leading to significant limitations.[3]

AKI is frequently associated with multiple organ dysfunction syndrome, which affects critically ill patients. Therefore, to better assess the influence of dynamic physiological variables and the effects of therapeutic interventions, longitudinal or sequential prognostic evaluations seem to be the most appropriate approach.[4]

In this study, a model of sequential and prospective evaluation of five general and three AKI-specific scores in critically ill patients was evaluated. We hypothesized that using a less strict definition of AKI could also improve the performance of severity scores and allow for better use of prognostic models starting at earlier stages of AKI.

RESULTS

A total of 2998 patients were admitted to the selected ICUs. The final sample size comprised 366 patients (Figure 1).

The AKI incidence was 19% (400 out of 2096 patients). Sepsis was the main cause of AKI (67%) and overall mortality was 67.8%. Nephrology consultations were requested by the ICU team for only 196 patients (53.5%) (Table 1).

Specific AKI scores criteria were met 1 day on average (0–2) after the AKI diagnosis day (D0), and this day was marked as D1. Nephrology consultations occurred 3 days[1–4] after D0, and this was marked D3. Table 2 shows clinical and laboratory data for the 3 days of analysis.

SAPS II (Simplified Acute Physiology Score II) was the general score with the best performance on all assessed days. The specific score with the best performance was SHARF (Stuivenberg Hospital Acute Renal Failure), followed by the
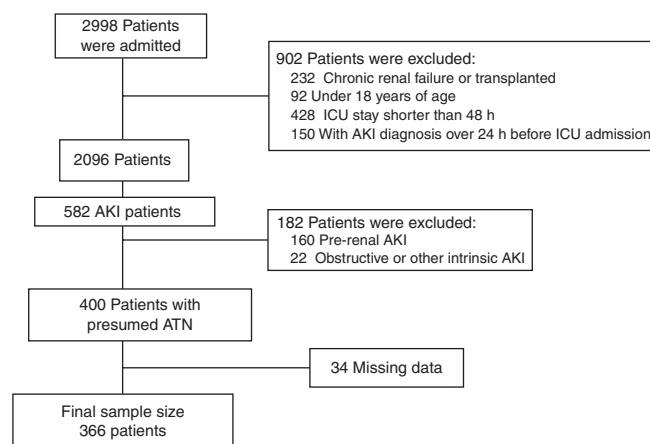
Figure 1 | Study population – a total of 2998 patients were admitted in the selected ICUs (intensive care units), resulting in a final sample of 366 patients with presumed ATN (acute tubular necrosis).

Table 1 | Patients' baseline characteristics

Variable	n	%
Demographic		
Age $\geqslant 60$ (years)	182	49.7
Men	216	59
Race/ethnicity		
Caucasian	253	69.1
African American	16	4.4
Asian	5	1.4
Mixed	92	25.1
Comorbidity		
CKD (stage III or above)	87	23
Hypertension	152	41.5
Heart failure	69	18.9
Coronary disease	28	7.7
Stroke	25	6.8
Peripheral vascular disease	13	3.6
Diabetes mellitus	85	23.2
COPD	24	6.6
Solid tumor	85	23.2
Leukemia/lymphoma	23	6.3
Liver disease	20	5.5
HIV positive	24	6.6
Clinical		
Sepsis	244	66.7
Nephrology consultation	196	53.5
Dialysis therapy	112	30.6

CKD, chronic kidney dysfunction; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

Liaño score (Table 3). A progressive improvement in scores' performance was seen. On D0, only SAPS II and SHARF scores presented satisfactory discrimination. On D1, these two indices and an additional three scores (Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and Liaño) reached the discriminatory threshold. On D3, all scores except Mehta presented good performance and two indices (SAPS II and SHARF) achieved an AUROC (area under the receiver operating characteristic curve) above 0.80. Calibration was good for all scores on all 3 days, except for Organ System Failure on D1 and Mehta on D3. Figures 2 and 3 show the discrimination and calibration curves for SAPS II and SHARF scores on all days of analysis.

DISCUSSION

This study shows a dynamic aspect for the prognostic scores in critically ill AKI patients. AKI is an inflammatory disease that usually comprises a multiple organ dysfunction syndrome that affects severely ill patients. These patients receive many therapeutic interventions (fluid resuscitation, antibiotics therapy, mechanical ventilation, nutritional support, glycemic control, etc.) with varying clinical responses. A great variation in physiological parameters and organ failure is expected. Our results clearly show the importance of assessing AKI as a dynamic and progressive process in which patients' assessments at any single moment may be inadequate. Another important aspect was the utilization of a less strict AKI definition, allowing for evaluation at earlier stages of the disease. Consequently, models provided for better performance since the beginning of the follow-up and prognostic scores achieved higher discriminatory accuracy compared with most earlier studies.[4–7] The PICARD study was the only one in which a similar sequential prospective evaluation was performed. However, that study reported unsatisfactory scores' performances, probably due to the utilization of a more strict AKI definition and population heterogeneity because of the multicenter nature of the study.

In this study, other factors may have contributed to the good scores' performances. Patients were evaluated by only one observer in a single academic institution. Additionally, only cases with presumed clinical acute tubular necrosis were enrolled and sepsis was found in about 70% of the sample, resulting in a more homogeneous population. In addition, only 8.5% of the patients were excluded (missing data), minimizing the risk of selection and analysis bias.

Furthermore, our hospital is a tertiary assistance institution and is a reference hospital for medical assistance and research, receiving mostly severely ill patients. On the other hand, this effect may have been partially minimized by the better care provided to these patients compared with other non-academic institutions.

In conclusion, general and specific scores with the best performance on all days of analysis were SAPS II and SHARF, respectively. Sequential and early evaluation seems to be a better approach for prognostic scoring systems in critically ill AKI patients.

PATIENTS AND METHODS

A prospective observational study was conducted through an active search for AKI cases by daily visits to six ICUs

Table 2 | Patients' characteristics on the day of AKI diagnosis (D0), the day when specific score criteria were met (D1), and the day of nephrology consultation (D3)

Parameter	Variable	D0 (N=366)	D1 (N=366)	D3 (N=366)
Organ failure	Number of organ failures	3.0 (2.0–4.0)	3.0 (1.0–3,0)	2.0 (1.0–3.0)*
	% CNS failure	47.8	50.9*	50*,†
	% Liver failure	50	52.8	49.2*
	% Cardiovascular failure	74.3	60.4	43.3*,†
	% Hematologic failure	9	10.8*	12*,†
	% Respiratory failure	73.8	74.7*	77.3*,†
	% Acute lung injury	72.4	72.5*	66.7*
	% ARDS	32.2	33.9*	30.1*,†
Physiological variables	Heart rate (per min)	100 ± 19	100 ± 17	98 ± 18*
	% Tachycardia	73	76*	73.8*,†
	Systolic BP (mm Hg)	120 (108–133)	121 (110–135)	127 (113–141)*
	Diastolic BP (mm Hg)	67 (60–75)	70 (60–76)	70 (62–80)*
	Mean arterial BP (mm Hg)	85 (77–93)	87 (78–96)	89 (80–99)*,†
	Temperature (°C)	36.5 (36–37)	36.5 (36–37)	36.5 (36–37)
	Urine output (ml/24 h)	1005 (523–1665)	945 (450–1570)	1030 (380–2000)
	% Oliguria (<400 ml/day)	18.6	22.5*	25.1
	% Furosemide use	25.1	24.9*	30.3*,†
	Respiratory rate	18 (14–23)	18 (14–23)	19 (15–23)
Laboratory variables	aAO2	149 (98–197)	148 (95–204)	127 (81–164)*,†
	Creatinine (mg/100 ml)	1.9 (1.5–2,6)	2.3 (2.0–3.0)	2.4 (1.6–3.5)*,†
	Urea (mg/100 ml)	74 (50–108)	93 (70–115)	98 (63–143)*,†
	pH	7.32 (7.24–7.39)	7.32 (7.24–7.38)	7.33 (7.25–7.39)
	Bicarbonate (mEq/l)	17 (14–20)	16 (13–19)*	16 (14–20)
	Lactate (mmol/100 ml)	19 (13–26)	19 (12–27)	17 (13–23)†
	Potassium (mEq/l)	4.4 (3.8–5.1)	4.6 (3.9–5.3)	4.4 (3.7–5.1)†
	Sodium (mEq/l)	140 (136–144)	141 (136–145)	142 (137–145)*
	Leukocyte (1000/mm³)	13.3 (9.0–19.0)	13.4 (9.0–18.8)	12.3 (8.4–18.8)
	Platelets (1000/mm³)	168 (101–274)	158 (90–253)*	151 (85–236)*
	% Thrombocytopenia (<150,000 platelets/mm³)	43.4	42.1*	49.7
	Hematocrit (%)	29 (26–34)	29 (26–34)	28 (24–32)*,†
	Total bilirubin (mg/100 ml)	0.8 (0.4–2.0)	0.8 (0.5–2.5)	0.8 (0.5–2.0)
	Enzymatic activity (%)	52 ± 22	50 ± 21	49 ± 24*
	GPT (UI/100 ml)	26 (16–62)	25 (14–61)	25 (13–55)*
	GOT (UI/100 ml)	42 (24–98)	43 (23–100)	39 (23–79)†
	Albumin (g/100 ml)	2.1 (1.8–2.6)	2.1 (1.7–2.5)	2.1 (1.7–2.6)*

aAO2, alveolar–arterial oxygen difference; ARDS, adult respiratory distress syndrome; BP, blood pressure; CNS, central nervous system; GOT, aspartate aminotransferases; GPT, alanine aminotransferases.
*$P < 0.05$ vs D0.
†$P < 0.05$ vs D1.

(Pneumology, Surgery, Trauma, Emergency, Internal medicine, and Infectious diseases), comprising 53 beds, in the University of São Paulo School of Medicine, Brazil. This hospital is a tertiary academic institution with 13 ICUs, totaling 128 beds. The study protocol was approved by the local ethics committee and an informed consent was not required.

Study population
All patients admitted to the selected ICUs were evaluated for renal function between November 2003 and June 2005. AKI was defined as an increase of $\geq 50\%$ on baseline serum creatinine. Only AKI cases diagnosed in the ICU or within the 24 h of admission were included. The exclusion criteria were baseline serum creatinine ≥ 3.0 mg/100 ml, previous dialysis, age <18 years, kidney transplantation, and ICU stay

for lesser than 48 h. Only cases of presumed acute tubular necrosis were considered. Sepsis was diagnosed according to established criteria.[8] Chronic kidney dysfunction was considered if an estimated creatinine clearance <60 ml/min per 1.73 m² was present (NKF (National Kidney Foundation) stage $\geq$ III).

Data variables
The collected variables were age, gender, race, hospital and ICU admission days, ICU origin, comorbidities, baseline renal function, presumed etiologies of AKI, vital signs, urine output, clinical events (sepsis, hypovolemia, bleeding, low cardiac output, cardiac arrest), laboratory studies, diagnostic and therapeutic procedures, including medications in use, nutritional support, vasoactive drugs, and mechanical ventilation. Multiple generic scores – Organ System Failure,[9]

Table 3 | Score values and area under the receiver operating characteristic (AUROC) curves for scoring systems on the day of AKI diagnosis (D0), the day when specific score criteria were met (D1), and the day of nephrology consultation (D3)

Scores	D0	D1	D3
Score values			
APACHE II	26.4 ± 7.0	27.5 ± 6.8*	27.9 ± 7.4*
SAPS II	53.0 ± 17.5	55.4 ± 17.3*	55.4 ± 19.2*
LODS	8.0 (6.0–10.0)	8.0 (6.0–10.0)	9.0 (6.0–11.0)*
OSF	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)
SOFA	10.0 (7.0–13.0)	10.0 (7.0–12.0)	11.0 (8.0–14.0)*,†
SHARF	181 (158–198)	180 (158–195)*	183 (161–198)†
Mehta	3.13 (2.29–4.37)	3.55 (2.69–4.44)*	3.74 (2.57–5.31)*
Liaño	0.49 ± 0.18	0.51 ± 0.18	0.48 ± 0.19†
AUROC			
APACHE II	0.66 ± 0.029	0.70 ± 0.031	0.77 ± 0.025*
SAPS II	0.73 ± 0.028	0.76 ± 0.030	0.83 ± 0.022*,†
LODS	0.63 ± 0.031	0.67 ± 0.033	0.79 ± 0.024*,†
OSF	0.64 ± 0.032	0.65 ± 0.035	0.71 ± 0.030*,†
SOFA	0.68 ± 0.030	0.70 ± 0.032	0.74 ± 0.027
SHARF	0.71 ± 0.031	0.75 ± 0.029	0.81 ± 0.026§
Mehta	0.51 ± 0.036‡	0.57 ± 0.037	0.63 ± 0.035¶
Liaño	0.67 ± 0.034	0.71 ± 0.032	0.77 ± 0.029**

APACHE, Acute Physiology and Chronic Health Evaluation; LODS, Logistic Organ Dysfunction Score; OSF, Organ System Failure; SAPS, Simplified Acute Physiology Score; SHARF, Stuivenberg Hospital Acute Renal Failure; SOFA, Sequential Organ Failure Assessment.
*$P < 0.05$ vs D0.
†$P < 0.05$ vs D1.
‡Asymptotic P=not significant.
§P=0.07.
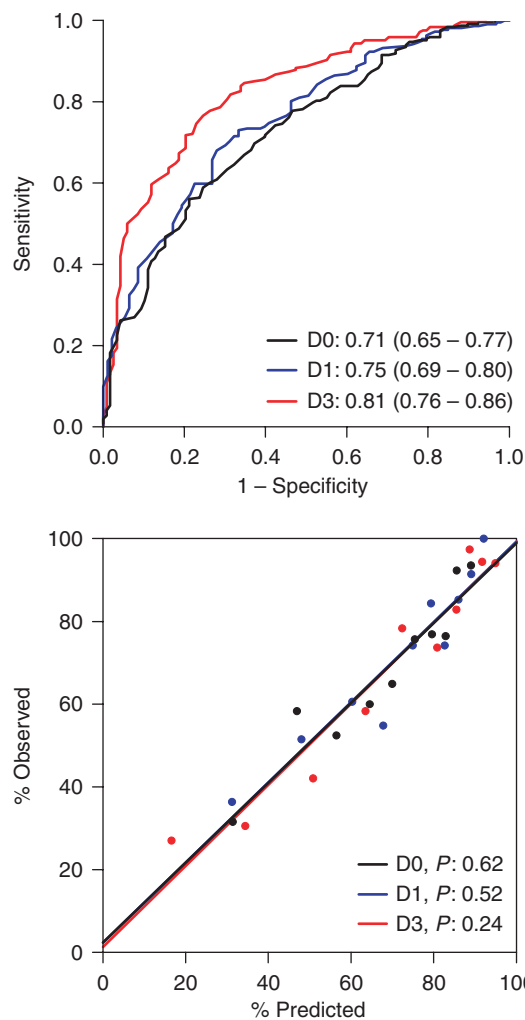¶P=0.051.
**P=0.08.

Figure 2 | Area under the ROC (receiver operating characteristic) curve (AUROC) and calibration curve for SHARF (Stuivenberg Hospital Acute Renal Failure) score on the day of AKI (acute kidney injury) diagnosis (D0), the day when specific score criteria were met (D1), and the day of nephrology consultation (D3).

Acute Physiology and Chronic Health Evaluation II,[10] SAPS II,[11] Sequential Organ Failure Assessment,[12] Logistic Organ Dysfunction Score[13]– and AKI-specific severity scores – SHARF,[14] Liaño,[15] and Mehta[1] – were calculated. Organ failure was defined as (a) respiratory – need of mechanical ventilation; (b) central nervous system – Glasgow scale $\leqslant 8$; (c) hepatic – total bilirubin $\geqslant 2.0\,mg/100\,ml$ and/or enzymatic activity $\leqslant 50\%$; (d) hematological – leukocytes $\leqslant 1000/mm^3$ and/or platelets $\leqslant 20,000$ and/or hematocrit $\leqslant 20\%$; (e) cardiovascular – cardiovascular Sequential Organ Failure Assessment score $\geqslant 3$.

Data collection strategy

Data were collected on the D0, D1, and D3. All patients were followed until hospital discharge or death. In-hospital mortality was the primary outcome. Data were collected by an observer not part of the ICU or nephrology staff. Nephrology consultation was solicited by the ICU physician.

Statistical analysis

All 366 patients (either referred or not referred to a nephrologist) were sequentially evaluated. The Kolmogorov–Smirnov normality test was applied for continuous and semi-continuous variables. Data with normal distributions are expressed as mean ± s.d. and were compared with an ANOVA (analysis of variance) test for repeated measures with Newman–Keuls post-test. Continuous variables without normal distribution are expressed as medians with 25th and 75th quartiles and were analyzed with the Friedmann test with a Müller–Dunn post-test. Categorical variables are expressed as proportions and were analyzed with Pearson's χ^2 test for independent groups and compared with the McNemar test. The discrimination of scores was assessed using the AUROC. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test comparing observed vs expected mortality across deciles of risk. Two-tailed P-values < 0.05 were considered significant. Statistical analysis was carried out by SPSS for Windows version 13.0 (Chicago, IL, USA).
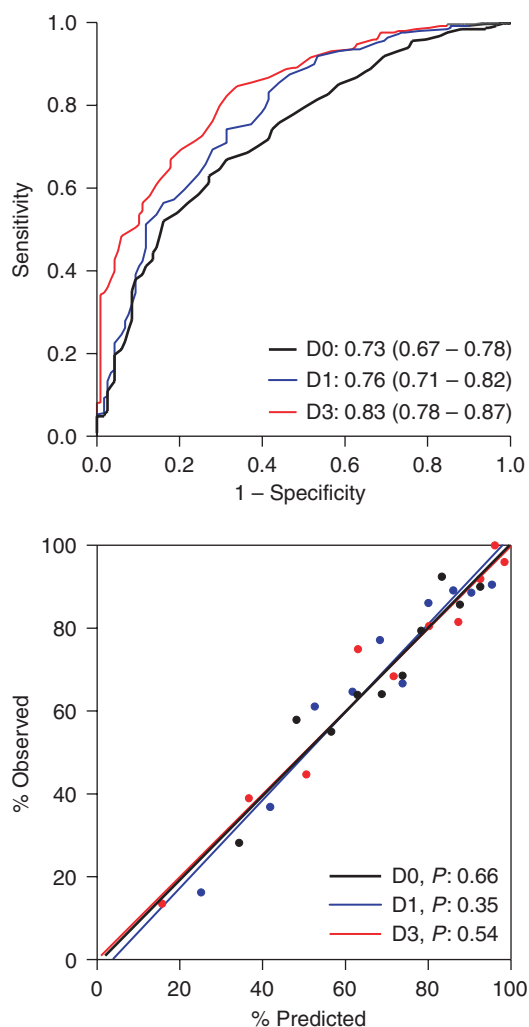
Figure 3 | Area under the ROC (receiver operating characteristic) curve (AUROC) and calibration curve for SAPS II (Simplified Acute Physiology Score II) score on the day of AKI (acute kidney injury) diagnosis (D0), the day when specific score criteria were met (D1), and the day of nephrology consultation (D3).

REFERENCES
1. Mehta RL, Pascual MT, Gruta CG *et al.* Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 2002; **13**: 1350–1357.
2. Bellomo R. The epidemiology of acute renal failure: 1975 versus 2005. *Curr Opin Crit Care* 2006; **12**: 557–560.
3. Uchino S. Outcome prediction for patients with acute kidney injury. *Nephron Clin Pract* 2008; **109**: 217–223.
4. Chertow GM, Soroko SH, Paganini EP *et al.* Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int* 2006; **70**: 1120–1126.
5. Douma CE, Redekop WK, VanderMeulen JHP *et al.* Predicting mortality in intensive care patients with acute renal failure treated with dialysis. *J Am Soc Nephrol* 1997; **8**: 111–117.
6. Fiaccadori E, Maggiore U, Lombardi M *et al.* Predicting patient outcome from acute renal failure comparing three general severity of illness scoring systems. *Kidney Int* 2000; **58**: 283–292.
7. Uchino S, Bellomo R, Morimatsu H *et al.* External validation of severity scoring systems for acute renal failure using a multinational database. *Crit Care Med* 2005; **33**: 1961–1967.
8. Bone RC, Balk RA, Cerra FB *et al.* American-college of chest physicians society of critical care medicine consensus conference – definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–874.
9. Knaus WA, Draper EA, Wagner DP *et al.* Prognosis in acute organ-system failure. *Ann Surg* 1985; **202**: 685–693.
10. Knaus WA, Draper EA, Wagner DP *et al.* APACHE II–a severity of disease classification-system. *Crit Care Med* 1985; **13**: 818–829.
11. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957–2963.
12. Vincent JL, Moreno R, Takala J *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707–710.
13. Le Gall JR, Klar J, Lemeshow S *et al.* The Logistic Organ Dysfunction System. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA* 1996; **276**: 802–810.
14. Lins RL, Elseviers M, Daelemans R *et al.* Prognostic value of a new scoring system for hospital mortality in acute renal failure. *Clin Nephrol* 2000; **53**: 10–17.
15. Liaño F, Garciamartin F, Gallego A *et al.* Easy and early prognosis in acute tubular-necrosis: a forward analysis of 228 cases. *Nephron* 1989; **51**: 307–313.