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Early detection of patients at high risk for acute kidney injury during disasters: development of a scoring system based on the Bam earthquake experience

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ABSTRACT

Background: **Early prophylactic hydration therapy in patients prone to acute kidney injury (AKI) can reduce its incidence in disasters. As sufficient availability of fluids might be problematic, it is important to discriminate those at risk versus not at risk for AKI. The present study uses biochemical findings from victims of the Bam earthquake to design decision rules for early detection of patients at risk for AKI.**
Methods: **Data were collected in hospitals admitting Bam earthquake victims. Biochemical factors on day 1 (creatinine, CPK, LDH, SGOT, uric acid, calcium, phosphorus, sodium, potassium, white blood cell count, platelet count) were introduced into multivariate models for prediction of AKI (serum creatinine >1.6 mg/dL) at a later stage.**
Results: **A rule of thumb to assess the absence of risk for AKI was developed, using ROC analysis: if on day 1, serum creatinine was <2 mg/dL, LDH was <2,000 IU and serum uric acid was <6 mg%, the risk for development of AKI was virtually nil. Using multiple regression analysis (0.45 CPK + 2.5 LDH + 2,700 K + 2,000 uric acid – 14,000)/10,000, was most predictive for serum creatinine on day 3. Dichotomizing this value at 2.0 yielded a sensitivity and specificity for prediction of AKI of 96.6% and 95.7%, respectively.**
Conclusions: **We propose 2 decision rules to predict development of AKI in earthquake victims. These scores can easily be calculated already at an early stage of a disaster, enabling rationalization of prophylactic hydration therapy in crushed earthquake victims.**

Key words: *Acute kidney injury, Acute renal failure, Bam earthquake, Crush injuries, Rhabdomyolysis*

INTRODUCTION

Acute kidney injury (AKI), as a component of the crush syndrome, is the second cause of death following disaster, after direct trauma (1, 2), although it can be prevented by early and vigorous intravenous fluid therapy (3, 4). In catastrophes such as earthquakes with a huge number of victims and a shortage of resources, it is for practical reasons impossible to administer high volumes of prophylactic hydration therapy to all victims. If rescue workers are confronted with a sudden influx of hundreds or thousands of victims, the patients in real need of intravenous fluid therapy should be prioritized. Therefore, it is essential to identify the risk of AKI in traumatized patients at an early stage, allowing the appropriate application of fluid therapy. The decision rules for this discrimination should be simple and straightforward, because first triage is most often done by rescue workers or general physicians without advanced skills in evaluating and monitoring fluid balance, specific knowledge of the crush syndrome and its consequences and without access to sophisticated medical equipment.

On December 26, 2003, an earthquake of 6.6 on the Richter scale struck the city of Bam, in southeastern Iran (5). More than 90% of Bam earthquake victims with severe trauma died on the scene of the catastrophe. Among the rescued victims, crush syndrome linked with AKI was the most important cause of morbidity and mortality (5).

The present study uses the biochemical findings from Bam earthquake victims to define new algorithms for the prediction of patients at risk for AKI in 2 different ways: a rule of

thumb to identify patients with a minimal risk of AKI and no need for specialized nephrological attention, and a score to assess the risk for AKI (AKI index) in patients who do need more specialized nephrological care.
These algorithms are important in planning prophylactic hydration therapy, which for the time being depends only on the physicians' expertise and judgment, as there might be a shortage of fluids, logistical equipment and medical staff in circumstances of calamity.

SUBJECTS AND METHODS

On the first day of the Bam earthquake, the Iranian Society of Nephrology, in collaboration with the International Society of Nephrology (ISN), developed a management protocol and a questionnaire and sent it to all hospitals expected to treat crush patients. The questionnaires were designed to register the basic demographic data and the key biological parameters of all rescued victims arriving in those hospitals. Biological data were selected for their wide and rapid availability at low cost. Development of AKI, serum creatinine levels on day 3, 10 basic biochemical values and the final outcomes for patients were registered. In addition, data were collected on details of the clinical course and surgical interventions.
In each hospital, a local key person was identified to assure the completeness and accuracy of the responses to the questionnaires, and the first author had regular contact by e-mail and telephone with all these key persons to cross-check accuracy of data. After completion of the data collection, data were entered into an SPSS database (version 11.5).
Data files were checked and validated against the questionnaires and finally analyzed by Stata (version 8.0).
In this study, AKI was defined as at least 2 reported serum creatinine values ≥1.6 mg/dL (≥141 μmol/L). All adult patients (aged ≥15 years) who were admitted in the first 3 days after the earthquake, who had a documented renal status (occurrence of AKI or not) and a measurement of serum creatinine level at day 3 were included in the analyses.
The registered biochemical factors were serum creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT), uric acid, calcium (Ca), phosphorus (P), sodium (Na), potassium (K), white blood cell count (WBC) and platelet count (Plt). Not all parameters were available in all patients, as parameters were collected according to local practices. For univariate analysis, all available results were used. For multivariate analysis, only patients with complete data sets for the investigated parameters were included.

Statistical analysis

Receiver operating characteristic curve and binary logistic regression analysis toward a rule of thumb

Receiver operating characteristic (ROC) curves for all individual parameters with regard to development of AKI were constructed using a univariate model, to decide the most discriminative cutoff point for each parameter. These were then combined to construct a rule of thumb for absence of risk for AKI, using binary logistic regression with the dichotomized parameters.

Linear regression analysis

The relationship between each biochemical factor and serum creatinine on day 3 was first investigated using linear regression. Stepwise multiple regression was used to develop a formula predicting serum creatinine at day 3. A ROC analysis of this estimated value was used to define an optimal cutoff point to dichotomize those developing AKI, defined as having at least 2 serum creatinine values >1.6 mg/dL, from those who did not.
The complete data set of all 10 parameters was present in 100 patients, and this patient group was used to develop the model, which was later tested in another 140 patients, who had complete data sets for CPK, LDH, potassium and uric acid, but not for the other 6 parameters, and who were thus not included in the population used to develop the AKI index.
In all analyses, α=0.05 was used as the level of significance.

RESULTS

For 1,441 patients (48% female) fulfilling the inclusion criteria, a questionnaire was filled out. Of these, 94 patients (6.5%) developed AKI (41% female), 68 of whom needed dialysis (41.5% female).
Although the questionnaire was distributed immediately after the earthquake, not all biochemical parameters were available in all patients, as can be expected in a situation of chaos. Table I lists the number of patients in

whom each specific biochemical value was obtained. These data were used to construct the univariate analyses.

Development of the rule of thumb excluding AKI

The results of the univariate logistic regressions using AKI as response, for each of the variables dichotomized according to the ROC curve analyses, are given in Table I. Using a stepwise multiple logistic regression model, we found that creatinine on day 1, LDH, and uric acid were the only significant predictors for development of AKI (Tab. II). Interestingly, for these 3 discriminative biochemical factors, the area under the ROC curves was greater than 0.95 already in the univariate analysis (Tab. I). Based on these analyses, a rule of thumb to define the risk for development of AKI was constructed: (a) if Cr ≥2 mg/dL, the patient is at high risk for development of AKI; and (b) if Cr <2 mg/dL, but LDH ≥2,000 IU and uric acid ≥6 mg/dL, the patient is also at high risk for development of AKI. Inversely, if on day 1, the serum creatinine is below 2 mg/dL, LDH is below 2,000 IU and serum uric acid is below 6 mg/dL, the patient risk for development of AKI is virtually zero.

TABLE I
ODDS RATIOS OF OCCURRENCE OF AKI

Biochemical factors	Number of patients	Odds ratio	SE	95% confidence interval	Cutoff	Area under the ROC curve	p Value
CPK (IU/L)	656	14.7	4.97	7.6-28.5	5,400	0.84	<0.0001
LDH (IU/L)	606	125.8	58.98	50.2-315.3	200	0.96	<0.0001
SGOT (IU/L)	342	45.2	23.48	16.4-125.1	195	0.92	<0.0001
WBC (/mm³)	1,311	7.2	1.83	4.3-11.8	12,500	0.79	<0.0001
PLT (/mm³)	1,220	2.2	0.57	1.4-3.7	150,000	0.42	0.001
Uric acid (mg/dL)	264	423.0	445.2	53.9-3,325.1	6	0.98	<0.0001
Sodium (mEq/L)	1,121	4.9	1.17	3.1-7.8	135	0.33	<0.0001
Potassium (mEq/L)	1,139	32.1	9.39	18.1-56.9	4.7	0.92	<0.0001
Calcium (mEq/L)	394	3.5	1.16	1.8-6.7	6	0.22	<0.0001
Phosphate (mEq/L)	364	18	7.47	7.9-40.6	4	0.85	<0.0001
Creatinine (mg/dL)	553	549.3	308.16	182.9-1,649.4	2	0.97	<0.0001

AKI = acute kidney injury; CPK = creatinine phosphokinase; LDH = lactate dehydrogenase; PLT = platelets; SE = standard error; SGOT = serum glutamic-oxaloacetic transaminase; WBC = white blood cells.

TABLE II
RESULT OF MULTIPLE LOGISTIC REGRESSION IN PREDICTION OF ACUTE KIDNEY INJURY

	Odds ratio	SE	95% confidence interval	p Value
LDH	21.2	30.00	1.3-333.9	0.030
Uric acid	37.3	57.62	1.8-766.4	0.019
Creatinine on day 1	61.3	86.78	3.8-982.6	0.004

Pseudo R^2=0.8451; p value of the fit = 0.3157 (Hosmer-Lemeshow).
LDH = lactate dehydrogenase; SE = standard error.

The sensitivity and specificity of this rule of thumb for prediction of AKI were 100% and 96.1%, and the positive and negative predictive values 82.6% and 100%, respectively.

Development of the AKI index

The relationship between the value of the biochemical factors and the serum creatinine level at day 3 after the earthquake was submitted to correlation and regression analysis. Although all individual correlations were found to be statistically significant, R^2 values were very low. The correlation was positive for serum creatinine, CPK, LDH, SGOT, WBC count, potassium, phosphate and uric acid, and negative for sodium, calcium and platelet count.

The biochemical factors were then submitted to stepwise multiple regression analysis for serum creatinine level at day 3. CPK, LDH, potassium and uric acid were retained as significant independent factors, whereas the other 6 parameters did not obtain sufficient significance to be entered in the model (Tab. III): estimated serum creatinine at day 3 = (0.45 CPK + 2.5 LDH + 2,700 potassium + 2,000 uric acid – 14,000)/10,000.

This value was used a surrogate marker for the risk of developing AKI later on.

Figure 1 shows the ROC curve in the test population. The area under the curve is 0.9917, showing the adequacy of the model. The point labeled D (corresponding to a value of 2) is the best cutoff, and we thus defined a patient predicted serum creatinine at day 3 of ≥2 mg/dL as a marker for high-risk patients. In the test population, the mean (±SD) of this value in AKI patients was 4 ± 1.3 mg/dL while in non-AKI patients it was 0.8 ± 0.5 mg/dL (p<0.0001). One hundred and twenty-two patients had a predicted serum creatinine at day 3 less than 2 mg/dL, and 18 patients scored above 2 mg/dL. In fact, 93.75% (15/16) of AKI patients and 2.4% (3/124) of non-AKI patients had a predicted serum creatinine at day 3 of more than 2 mg/dL (p<0.0001). The sensitivity and specificity for AKI prediction was 96.6% and 95.7%, respectively, and the positive predictive value was 0.83 (15/18), whereas the negative predictive value was 0.99 (1/122).

The sensitivity and specificity of a patient predicted serum creatinine at day 3 ≥2 mg/dL for prediction of complications and associated events were as follows: sepsis 60% and 85.4%; disseminated intravascular coagulation 66.7% and 85.1%; fasciotomy 85% and 91.1%; and death 75% and 86.5%.

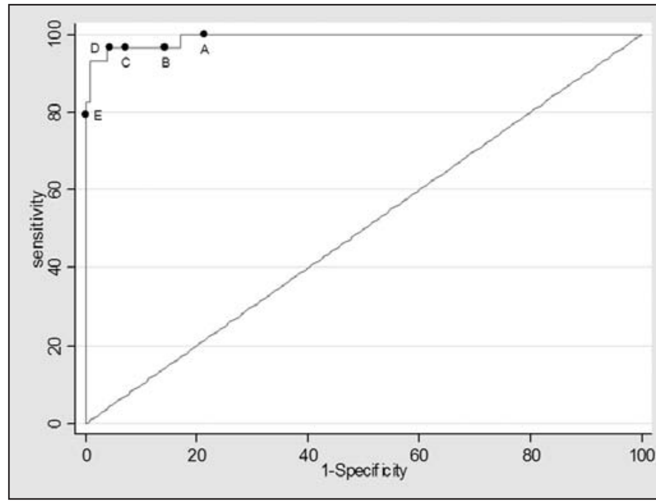

Fig. 1 - Receiver operating characteristic (ROC) curve of estimated serum creatinine at day 3 in the test group, as a parameter to predict development of acute kidney injury. Area under ROC curve = 0.9917. Values of estimated serum creatinine at day 3: A=1.1, B=1.3, C=1.6, D=2.0 and E=3.0.

TABLE III

MULTIPLE REGRESSION ANALYSIS FOR SERUM CREATININE AT DAY 3

Biochemical factors	Regression coefficient	Standard error	p Value
CPK	0.000045	0.0000108	<0.0001
LDH	0.0002549	0.0000564	<0.0001
Potassium	0.2714466	0.0851457	0.02
Uric acid	0.2040066	0.037655	<0.0001
Regression constant	-1.394363	0.3582819	<0.0001

R^2=0.79.
CPK = creatinine phosphokinase; LDH = lactate dehydrogenase.

Discussion

Based on 3 easily available biochemical data, a rule of thumb to detect victims without risk for AKI was developed: if on day 1, serum creatinine was below 2 mg/dL, LDH below 2,000 IU and serum uric acid below 6 mg/dL, the probability of developing AKI was virtually zero. Vice versa, a value for the equation (0.45 CPK + 2.5 LDH + 2,700 K + 2,000 uric acid – 14,000) 10,000 of >2.0 was most appropriate to distinguish victims at risk, from those not at risk for AKI.

In combination, the 2 algorithms presented here allow the attending medical personnel to already judge the risk for AKI on the first day of a disaster, and this based on simple biochemical parameters that can easily be made available even in disaster situations. Of course, these decision rules need further validation in larger patient groups and different earthquake situations.

Acute kidney injury (AKI) is an important complication of the crush syndrome, with a high morbidity and mortality. Prevention of AKI in this condition is possible by early and aggressive fluid therapy (4). However, in circumstances of disaster, logistic supplies are often insufficient to cover fluid therapy in all victims. Discrimination of patients at risk from those not at risk is thus essential for success in management of crush syndrome.

Earthquakes all over the world are among the main causes of crush syndrome (6-8) with rhabdomyolysis-induced AKI as their most important complication, carrying a high mortality rate. AKI in this setting is to a large extent preventable with forced alkaline diuresis (4). The exact therapeutic approaches to be followed in these cases remain a matter of debate, however (2). For example, suggestions for the appropriate amount of fluid vary from only 3 L/day (1), to up to 1.5 L/hour with a minimum of 12 L/day (2, 9). In a situation of calamity, not enough fluids and monitoring tools are available to treat all victims, and under these circumstances, scores that can estimate the risk of developing AKI, or rules of thumb which can identify patients not at risk for AKI, can be of great help. These scoring systems should be easy to use in emergency situations, and should therefore rely on simple clinical or biochemical parameters.

Several laboratory values have already been tested to determine a potential association with the development of AKI (10-12) in patients with nontraumatic rhabdomyolysis. Usually traumatic rhabdomyolysis patients have a high prevalence of compartment syndrome, second wave phenomena, amputation, dehydration and hypotension, resulting in a different picture from what is seen in the nontraumatic variant (1, 5). Our paper is the first to present new algorithms for prediction of AKI in earthquake victims, based on a database collected in the aftermath of the Bam earthquake. These algorithms will be useful to alert for potential risk of crush injury–related AKI, especially in patients who show only limited muscular damage externally. Using the rule of thumb, patients not at risk for AKI can be identified, so that more care can be directed to the others. In earthquake disasters, crush victims needing dialysis are mostly centralized in hospitals which are remote from the affected area, since local dialysis facilities are mostly destroyed. Patients at risk for AKI should be transferred to these centers as soon as possible, but often the roads are also blocked or damaged and transport is therefore cumbersome. In addition, specialized nephrological care for crush-related AKI is scarce in any case. Therefore, detection of victims who have no risk for AKI, and can thus be easily and safely managed in local hospitals, is crucial. Our simple rule of thumb can be of help in deciding on referral of victims to specialized nephrological care centers.

Although the parameters were selected by mathematical modeling, all 3 of them are closely linked to the underlying pathophysiology of (13).

The more complex AKI index formula on the other hand not only allows predictions for developing AKI, but gives also an estimate of that risk, and of the severity of the subsequent complicating events, such as sepsis, disseminated intravascular coagulation, fasciotomy and death.

Our study has a number of limitations. The lack of scrutiny in collecting complete data sets is a potential flaw. However, this survey was not intended to offer a description of the epidemiology of AKI after an earthquake. The major purpose was the construction of discriminatory rules allowing us to discriminate patients at risk versus those not at risk of AKI in a disaster situation, and therefore we used only parameters that are easily available and reliable even in tough conditions. Whereas not all data sets were complete, a substantial effort has been made to ensure that the data in the database were those that were available to the clinicians at the time of the disaster, by cross-checking all data with the original paper files. There is no evidence that data were missing in a biased way, as they were missing at random, as a consequence of the chaotic situation.

Another potential drawback is that the rule of thumb was tested only in a limited population. Corroboration of the decision rules in other earthquake conditions and using the currently available treatment flow charts for rehydration is certainly warranted, but this can of course only be done if

the decision rules are first made widely available, so that they can be used in forthcoming earthquake conditions.
In view of the recently published RIFLE criteria for AKI, our definition of AKI as a serum creatinine of more than 1.6 mg/dL can be questioned. However, because in disaster conditions, previous creatinine values are not available, the RIFLE classification (14) unfortunately can not be applied strictly to this type of population. However, it is well established that especially patients in the "injury" category have a high risk for further deterioration of renal function (15). Taking all this into account, our decision to use >1.6 mg% of serum creatinine as a fixed criterion to approximate a >50% increase of serum creatinine in all patients seems reasonable, as this in our opinion most closely conforms to the "injury" category of the RIFLE criteria (14).

Conclusions

Decision rules to discriminate patients at risk for AKI after crush are proposed. These algorithms allow a timely installment of appropriate treatment and effective prophylactic hydration in those who are really in need of such treatment, and give a general idea of the severity of the risk for development of AKI. Implemented in this way, they can improve not only the outcome for the individual patient, but also the general prevention and management of AKI in earthquake situations. Further validation of these decision rules in other patient groups is warranted.

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