Prognostic Value of Serum Creatinine in Traumatic Brain Injury
Valor Prognóstico da Creatinina Sérica no Traumatismo Cranioencefálico

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is a complex event, plenty of populational and regional peculiarities, with multiple causes and different levels of severity, having a wide range of prognosis. Objectives: To present and identify the prognostic association of serum creatinine dosage at admission of TBI patients in the Triângulo Mineiro region, Brazil. Methods: Quantitative, retrospective and documental study based on the analysis of medical records of TBI patients presented at the Clinics Hospital of Federal University of Triângulo Mineiro in the city of Uberaba, Brazil, from January 2007 to December 2017. Results: A total of 794 TBI patients were included. The mean value of serum creatinine was higher in males with severe TBI, altered CT, subdural hematoma, brain swelling, pneumocephalus, and death outcome, and with increasing values the higher the age range. Serum creatinine was also independently associated with the death outcome (after adjustment through multivariate logistic regression) (CR: 1.64; CI: 1.25-2.15). The serum creatinine value of 1.18 mg/dL represented the cutoff point of best specificity (89.12%; CI: 86.4-91.5) and sensitivity (42.13%; CI: 34.8-49.7). Conclusions: Serum creatinine was independently associated with the death outcome, proving to be a promising laboratory predictor of TBI.

Keywords: Traumatic Brain Injuries; Creatinine; Prognosis

RESUMO

Introdução: O traumatismo cranioencefálico (TCE) é uma entidade complexa, carregada de peculiaridades populacionais e regionais, com múltiplas causas e diferentes níveis de gravidade, tendo uma vasta gama de prognósticos. Objetivos: Apresentar e identificar a associação prognóstica da dosagem de creatinina sérica na admissão de doentes com TCE na região do Triângulo Mineiro, Brasil. Métodos: Estudo quantitativo, retrospectivo e documental baseado na análise dos registos médicos de doentes com TCE atendidos no Hospital das Clínicas da Universidade Federal do Triângulo Mineiro na cidade de Uberaba, Brasil, de Janeiro de 2007 a Dezembro de 2017. Resultados: Foi incluído um total de 794 pacientes com TCE. O valor médio da creatinina sérica era maires elevado nos homens com TCE grave, TAC alterada, hematoma subdural, inchaço cerebral, pneumocefalia, e resultado de morte, além de valores crescentes...
Among the several attempts to conceptualize traumatic brain injury (TBI), one of the most objective and short one defines it as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Its alarming epidemiological data do not generate uncertainty about TBI. TBI is already the leading cause of mortality in people under 40 years of age. According to estimates by the World Health Organization (WHO), 15 million people are victims of TBI every year (deaths or hospitalizations), and the disease may become the leading cause of death and disability by 2030. In all scenarios, the male gender is the most affected. It is, therefore, a critical global public health problem that deserves special attention. However, research related to TBI at global level needs to be contextualized, as different regions have their own needs and obstacles. Successful interventions in some regions may not be a priority for others, given their regional peculiarities.

In poor and developing countries, such as Brazil, where TBI, in addition to having a significant socioeconomic impact also has a high prevalence and increasing incidence rates, studies on the subject are still scarce. Thus, the knowledge of regional and populational particularities associated with TBI tracing its epidemiological profile, may be useful to prevent its predominant causes to assist in treatment and establish prognosis.

In an attempt to identify the prognostic factors of TBI, two classic studies deserve to be highlighted. The Corticosteroid Randomization After Significant Head Injury (CRASH) (2008) sought to identify the probability of death after 14 days of TBI and the possibility of neurological sequelae after 6 months of trauma, and The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) (2008) revealed as independent prognostic variables: age, Glasgow Coma Scale, pupil response and the tomographic characteristics of TBI. Both had data collected within the first 24 hours of TBI. Many studies have reported the prognostic value of clinical and radiological parameters in TBI, but relatively few have investigated the relationship between laboratory parameters at admission and the final outcome of patients.

Van Beek et al. (2007) stated that the presence of coagulopathy, hyperglycemia and anemia are clearly related to worse prognosis. They also conclude that laboratory parameters, routinely determined at admission, are important predictors of outcome after TBI. In this field, it is noteworthy that in TBI patients, the brain self-regulation and renal function are frequently impaired. The brain and kidneys, by means of the self-regulation mechanism, present a common and unique way of reacting to fluctuations in blood pressure and blood flow, due to similar low vascular resistance in both. Thus, information on microvascular damage in one organ can provide information on damage in the other organ. This dialogue between kidneys and brain remains an area with very few publications, despite its clinical relevance. Castro et al. (2018) proposed that the rapid evaluation of serum markers of renal dysfunction can be used as a substitute for...
the integrity of cerebral microvascular function, inferring prognosis, while it can help to identify individuals at high risk for complications and possibly provide therapeutic targets in the future. To estimate renal function, serum creatinine levels continue to be a low-cost, high-sensitivity test, despite its low sensitivity\(^\text{14,15}\). It is currently one of the most requested biological dosages in clinical practice worldwide\(^\text{16}\).

Creatinine history dates back to 1847, when Justus von Liebig, for the first time, used the term creatinine to name a substance obtained after heating mineral salts\(^\text{14,17}\). However, it was the Danish physiologists Rehberg and Holten, in mid-1920, who studied the relationship between creatinine, more specifically its clearance, and renal function\(^\text{18}\). Through colorimetric methods derived from the classical reaction of Jaffè (1886) (picrate and creatinine which in alkaline medium gives a red-orange solution) or enzymatic methods described by Dubbos and Miller (1937), creatinine can be measured in blood and urine\(^\text{14}\). However, both methods are susceptible to various interferences and the method considered as ideal is the isotopic dilution mass spectrometry, which is not widely used due to its high cost\(^\text{19}\).

Creatinine is a terminal catabolite, physiologically inert, synthesized from creatine available in muscles (98%), kidneys, brain and liver after an irreversible and non-enzymatic reaction\(^\text{20,21}\). The understanding of creatinine physiology necessarily depends on the knowledge of creatine. The latter is the result of methylation in the liver of guanidinoacetic acid, which is a product of the reaction between glycine and arginine, a reaction that occurs in the kidneys, small intestine, pancreas, brain, mammary gland and liver\(^\text{22,23}\). Because of high availability of creatine in muscles, the differences that can be observed in creatinine concentrations in men and women, the elderly and young people, and individuals from different ethnic groups are, therefore, mainly explained, in the absence of renal disease, by differences in muscle mass between these groups\(^\text{24}\). In healthy patients, the constant production of creatinine is equal to its urinary excretion, because the extra-renal excretion is insignificant, and urinary clearance with an indicator of glomerular function is used\(^\text{25}\). The existing hemodynamic parallelism between cerebral and renal vascular beds suggests a supposed connection between the brain and kidneys. Both organs are highly perfused and have low vascular resistance. If not for the mechanism of self-regulation, variations in blood flow throughout the cardiac cycle would be exposed\(^\text{26,27}\). This refined myogenic mechanism, called self-regulation, works as a generalized vascular protection mechanism. It is an inherent capacity of the vascular bed to maintain constant perfusion, despite variations in blood pressure and intracranial pressure, and it is important to maintain relatively constant the cerebral and renal blood flow\(^\text{13,28}\).

Additionally, both the brain and kidneys play an important role in maintaining homeostasis and hydroelectrolyte balance. It is believed that the mediators of this dialogue between kidneys and brain include hormones, baroreceptors, osmoreceptors, and direct inter-organ innervation\(^\text{12,29}\). Based on these facts, the objective of this article is to present and identify the prognostic association of serum creatinine dosage on admission of TBI patients in the region of the South Triângulo Mineiro, Brazil.

METHODS

This is a quantitative, retrospective and documentary study, based on the analysis of electronic and physical records of TBI patients presented at the Clinics Hospital of Federal University of Triângulo Mineiro, Uberaba, Brazil, from January 2007 to December 2017. Exclusion criteria were: absence of identification data (name and identification number of hospital records), absence of demographic data (gender and age), absence of admission data (date of hospital admission and Glasgow Coma Scale score at admission inferring the severity of TBI), absence of outcome data (date of hospital discharge or death of the patient). The creatinine dosage was performed through the colorimetric method in the COBAS 6000 device - Module C501 (Roche-Hitachi\(^\text{®}\)).

After collecting data, this was input in Microsoft Excel 2016\(^\text{®}\) program. Subsequently, it was organized and analyzed using the Statistical Package for Social Sciences\(^\text{®}\) for Windows.
From a total of 1347 patients, 794 (58.9%) who presented serum creatinine dosage in the first 24 hours of hospitalization were selected. It was observed that creatinine showed a median value of 0.85mg/dL (p25:68; p75:1.06) with a mean of 1.0 mg/dL (0.95-1.06) (Table 1).

Table 1. Serum creatinine dosage median (mg/dL), within 24 hours of admission.

| Variable                        | Total (%) |
|---------------------------------|-----------|
| Number of patients              | 1347 (100%) |
| Serum creatinine                | 794 (58.9%) |
| Median and interquartile range (p25-p75) | 0.85 (0.68-1.06) |
| Average (IC: 95%)               | 1.0mg/dL (0.95-1.06) |

Note: Serum creatinine dosage: unit (mg/dL).

Demographic data and creatinine
In all TBI patients submitted to serum creatinine dosage, in the first 24 hours, there was a statistical difference related to gender. In addition to predominance in males (83%; p<0.001), they presented higher median (0.88 mg/dL (0.72-1.09)) and mean (0.93 mg/dL (0.89-0.96)) values in relation to females (Table 2).

Table 2. Distribution and median value of serum creatinine dosage (mg/dL) within 24 hours of admission.

| Variable                        | Gender             | P     |
|---------------------------------|--------------------|-------|
|                                 | Male (%)           | Female (%) |<0.001|
| Serum creatinine                | 659 (83.0%)        | 135 (17.0%) |
| Median (p25-p75)                | 0.88               | 0.68 |
|                                 | (0.72-1.09)        | (0.61-0.83) |
| Average (IC 95%)                | 0.93               | 0.68 |
|                                 | (0.89-0.96)        | (0.63-0.73) |

Note: Serum creatinine dosage: unit (mg/dL); p: degree of significance.
Regarding the age group, it was observed that the mean value of serum creatinine was higher in direct proportion to the age group. The same significance was not observed in relation to the day of the week of hospital admission (Graph 1 and Table 3).

**Graph 1.** Mean value of serum creatinine dosage (mg/dL), within 24 hours of admission.

![Graph showing mean serum creatinine by age group](image)

**Table 3.** Mean value of serum creatinine dosage (mg/dL), in the first 24 hours of admission.

| Variable       | Average (mg/dL) | CI 95%    | P   |
|----------------|----------------|----------|-----|
| Gender         |                |          |     |
| Female         | 0.68<sup>a</sup> | 0.63     | 0.73|
| Male           | 0.93<sup>b</sup> | 0.89     | 0.96|
| Age Group      |                |          |     |
| Children       | 0.47<sup>a</sup> | 0.42     | 0.53|
| Youngs         | 0.85<sup>b</sup> | 0.80     | 0.91|
| Young Adults   | 0.85<sup>c</sup> | 0.85     | 0.94|
| Adults         | 0.93<sup>c</sup> | 0.88     | 0.98|
| Elderly        | 0.47<sup>a</sup> | 0.42     | 0.53|
| Admission Day  |                |          |     |
| Sunday         | 0.83           | 0.78     | 0.90|
| Monday         | 0.87           | 0.80     | 0.95|
| Tuesday        | 0.92           | 0.84     | 1.00|
| Wednesday      | 0.95           | 0.86     | 1.04|
| Thursday       | 0.91           | 0.83     | 1.00|
| Friday         | 0.85           | 0.77     | 0.94|
| Saturday       | 0.85           | 0.79     | 0.92|

Note: Serum creatinine dosage: unit (mg/dL); a, b, c, d: in each variable, distinct letters denote statistical difference; CI: confidence interval; p: degree of significance
Etiological data and creatinine

There was no statistical difference between the mean values of serum creatinine dosage and the etiological data (Table 4).

Table 4. Mean value of serum creatinine dosage (mg/dL) within 24 hours of admission.

| Variable                  | Average (mg/dL) | CI 95% | P       |
|---------------------------|-----------------|--------|---------|
| General Cause             | 0.590           |        |         |
| Traffic                   | 0.87            | 0.83   | 0.91    |
| Fall                      | 0.92            | 0.85   | 0.98    |
| Violence                  | 0.86            | 0.79   | 0.94    |
| NS                        | 0.86            | 0.75   | 0.98    |
| Specific Cause            | 0.129           |        |         |
| Gunshot wound             | 0.90            | 0.75   | 1.08    |
| Physical aggression       | 0.83            | 0.75   | 0.93    |
| Pedestrian collision      | 0.75            | 0.68   | 0.82    |
| Bicycle                   | 0.97            | 0.83   | 1.15    |
| Truck                     | 0.88            | 0.61   | 1.27    |
| Car                       | 0.88            | 0.82   | 0.95    |
| Cart                      | 0.77            | 0.31   | 1.86    |
| Fall from height          | 0.95            | 0.86   | 1.04    |
| Stab wound                | 0.91            | 0.74   | 1.11    |
| Shallow-water diving      | 0.80            | 0.48   | 1.33    |
| Motorcycle                | 0.91            | 0.85   | 0.97    |
| NS                        | 0.86            | 0.75   | 0.98    |
| Fall from own height      | 0.88            | 0.79   | 0.98    |

Note: Serum creatinine dosage: unit (mg/dL); CI: confidence interval; p: degree of significance; NS: not specified.
**Tomographic data and creatinine**

Regarding tomographic data, the description of altered tomography, presence of subdural hematoma, brain swelling or pneumocephalus were significantly related to higher mean serum creatinine dosage with reference to the non-existence of these changes (Table 5).

| Variable                      | Average (mg/dL) | CI 95%      | P     |
|-------------------------------|-----------------|-------------|-------|
| Alterated CT                  | 0.89            | 0.86-0.92   | 0.049 |
| Contusion CT                  | 0.86            | 0.81-0.91   | 0.408 |
| EH CT                         | 0.84            | 0.76-0.92   | 0.311 |
| SH CT                         | 0.99            | 0.93-1.06   | <0.001|
| Intraventricular Hemorrhage TC| 0.95            | 0.77-1.16   | 0.449 |
| DAL CT                        | 0.95            | 0.91-1.06   | 0.002 |
| TSH CT                        | 0.89            | 0.79-1.00   | 0.58  |
| Brain Swelling CT             | 0.93            | 0.87-0.99   | 0.99  |
| Pneumocephalus CT             | 0.93            | 0.95-1.25   | <0.001|
| Fracture CT                   | 0.86            | 0.81-0.92   | 0.541 |

Note: Serum creatinine dosage: unit (mg/dL); CT: skull computed tomography; EH: extradural hematoma; SH: subdural hematoma; DAL: diffuse axonal lesion; TSH: traumatic subarachnoid hemorrhage; CI: confidence interval; p: degree of significance.

**Clinical data and creatinine**

Regarding the clinical data, severe TBI presented higher mean serum creatinine value when compared to mild and moderate TBI (Graph 2).
The other clinical variables such as presence, number or location of associated trauma and also the need or not for neurosurgery were not associated with the laboratory test in question (Table 6).

Table 6. Mean value of serum creatinine dosage (mg/dL) within 24 hours of admission.

| Variable               | Average (mg/dl) | CI 95%  | P     |
|------------------------|-----------------|---------|-------|
| TBI Severity           |                 |         | 0.002 |
| Mild a                 | 0.85            | 0.81    | 0.89  |
| Moderate b             | 0.81            | 0.75    | 0.88  |
| Severe                 | 0.94            | 0.89    | 0.99  |
| Neurosurgery           |                 |         | 0.143 |
| No                     | 0.87            | 0.83    | 0.90  |
| Yes                    | 0.91            | 0.86    | 0.97  |
| Associated trauma      |                 |         | 0.289 |
| No                     | 0.86            | 0.83    | 0.90  |
| Yes                    | 0.90            | 0.85    | 0.94  |
| Number of associated trauma |         |         | 0.841 |
| 1                      | 0.89            | 0.84    | 0.95  |
| 2                      | 0.91            | 0.83    | 1.0   |
| 3                      | 0.94            | 0.79    | 1.13  |
| Topography of associated trauma |       |         | 0.112 |
| NR                     | 0.87            | 0.83    | 0.90  |
| Abdomen                | 1.04            | 0.84    | 1.28  |
| Face                   | 0.91            | 0.80    | 1.02  |
| Orthopedics            | 0.85            | 0.78    | 0.92  |
| Soft tissues           | 0.73            | 0.57    | 0.94  |
| Thorax                 | 0.96            | 0.88    | 1.06  |
| Spinal injury          | 0.85            | 0.74    | 0.98  |

Note: Serum creatinine dosage: unit (mg/dL); a, b: in each variable, distinct letters denote statistical difference; CI: confidence interval; p: degree of significance; NR: not reported.
Death outcome and creatinine

The death outcome had a mean serum creatinine significantly higher than the non-death outcome (Table 7).

### Table 7. Mean value of serum creatinine dosage (mg/dL) within 24 hours of admission.

| Variable | Average (mg/dl) | CI 95% | p       |
|----------|-----------------|--------|---------|
| Death    |                 |        | <0.001  |
| Yes      | 1.13            | 1.06   | 1.20    |
| No       | 0.82            | 0.79   | 0.85    |

Note: Serum creatinine dosage: unit (mg/dL); CI: confidence interval; p: degree of significance.

### Table 8. Multivariate analysis of serum creatinine dosage (mg/dL) within 24 hours of admission.

| Variable | P       | OR  | CI 95% |
|----------|---------|-----|--------|
| Creatinine<sup>#</sup> | <0.001  | 2.0 | 1.5    | 2.6    |
| Creatinine<sup>£</sup> | <0.001  | 1.64| 1.25   | 1.15   |

Note: Serum creatinine dosage: unit (mg/dL); CI: confidence interval; p: degree of significance; OR: odds ratio; # Univariate logistic regression - serum creatinine dosage; £ Multivariate logistic regression - serum creatinine dosage adjusted for sex, age group, cause of trauma, severity of TBI, altered CT, neurosurgery and associated trauma.

The value of serum creatinine dosage of 1.18 mg/dL represented the cutoff point of best specificity (89.12%; CI: 86.4-91.5) and sensitivity (42.13%; CI: 34.8-49.7) related to death. Representing accuracy close to satisfactory (70%), with an area under the “ROC” curve of 67.2% (CI: 63.9-70.5; p<0.0001) (Graph 3).
DISCUSSION

Although there are few publications associating kidneys and brain, the consequences of renal failure on the central and peripheral nervous systems are well known, especially in patients under dialysis, such as cognitive decline, cerebrovascular events and peripheral neuropathy\textsuperscript{12,30}. Little is known about brain disease predicting the outcome of kidney function. Normal kidney function is mediated by homeostasis of the entire body, including neuronal homeostasis\textsuperscript{12}. In a study of 142 patients, Kobayashi et al., (2010)\textsuperscript{31} showed that subclinical brain lesions (such as silent brain infarctions) are an independent prognostic factor for the progression of renal disease. This communication pathway from the brain to the kidneys is still not clear. According to Lu et al. (2015)\textsuperscript{24}, during acute brain injury, the brain and kidneys can interact by amplifying cytokine induced damage, leukocyte leakage, oxidative stress and deregulation of sodium, potassium and water channels. In TBI patients the brain self-regulation and kidney function are often impaired\textsuperscript{10}. In these patients, brain injury associated with their loss of self-regulation may contribute to the impairment of renal self-regulation and its dysfunction, leading to a decrease in renal clearance of creatinine, with greater susceptibility to develop acute kidney injury\textsuperscript{27}.

Acute kidney injury contributes to the increased permeability of the blood-brain barrier, which already occurs in TBI. In addition, it leads to an increase in pro-inflammatory cerebral mediators and hydroelectrolyte imbalance, which, associated with barrier dysfunction, results in higher water inflow and consequent cerebral edema\textsuperscript{12,24,32}. In such patients, in addition to the endocrine metabolic and immunological response to trauma triggered by brain injury, vasopressor support and the use of hypertonic solutions, frequently used in TBI victims, it can promote blood flow disruption and the worsening of renal excretory function, leading to positive feedback of cerebral edema\textsuperscript{27,33,34}. Nongnuch et al. (2014)\textsuperscript{26} driven attention to the increased activity of the sympathetic nervous system and inflammatory state as common pathways between acute brain injury and acute renal injury. It is suggested that an unknown serum element to be present, playing an important role in this connection, whether cytokines, neurotransmitters, renal and brain renin-angiotensin systems, vasopressin or autonomic neural control\textsuperscript{33,35,36}.

Graph 3. “ROC” curve, demonstrating sensitivity and specificity of serum creatinine dosage for death outcome.

Note: area below the curve: 67.2%; CI: 63.9-70.5; p<0.0001
The experimental study by Rhee et al. (2012) suggested that renal self-regulation is probably more fragile compared to that of the brain because renal blood flow becomes passive to pressure before cerebral blood flow. When comparing self-regulation of the brain and kidneys in pigs, they observed that small pressure variations caused by hemorrhage were already sufficient for the loss of revascular reactivity. To estimate this renal function, currently, most Intensive Care Units (ICUs) worldwide still use the daily serum creatinine dosage as an endogenous substance to estimate renal function, due to its high specificity and low cost, despite its low sensitivity. This fact stimulated the present study.

On the other hand, in early stages (perhaps as a protective function), increased glomerular filtration rate with increased renal clearance and polyuria are also frequent findings in severely ill patients, such as in polytraumatized patients and, in particular, in young TBI victims. This increase in renal clearance is significantly related to better cerebral self-regulation and associated with better outcome in patients with TBI.

At the São João Hospital, in the city of Porto, Portugal, Dias et al. (2015) in a study of 46 patients with ischemic stroke, found a mean serum creatinine value of 0.6 mg/dL (95% CI: 0.2-1.7). In a multicenter study conducted by Udy et al. (2014), with 932 patients of which 12.8% were victims of trauma, the mean creatinine value was 0.81 mg/dL (95% CI: 0.78-0.84). The presence of increased renal clearance in the first 24 hours of admission significantly predicted the sustained elevation of creatinine clearance in these patients during the first week in the ICU. According to the authors, this increase in the renal clearance of creatinine may represent an "expected" response to systemic inflammation.

Although no reported study was conducted exclusively with TBI victims, values close to those reported in the world literature were found in the present study, which showed a median serum creatinine value of 0.85mg/dL, corroborating for the validity of subsequent correlations. The study also showed higher mean values of serum creatinine dosage in males. Additionally, serum creatinine was also higher in direct proportion to the age group of TBI victims. In general, these differences are reported in the current literature.

Therefore, considering the high availability of creatine (creatinine precursor) in muscles, the differences which can be observed in creatinine concentrations between gender, and in the elderly and young people are mainly explained, in the absence of renal disease, by differences in muscle mass between these groups.

Severe brain damage is known to trigger immunological consequences of multiple organs. As a result, Baptista (2013) studying the evolution of kidney transplantation and the characteristics of the deceased donor demonstrated that the donor creatinine, collected immediately before the extraction of the organ, when higher than 1.5mg/dL, was a risk factor for a worse outcome of the transplant, confirming the data of Port et al., (2002). Following this reasoning, the current study demonstrated that there was a significant association between the increasing of serum creatinine dosages related both to the death outcome and to the severity of TBI and the existence of tomographic alteration. In patients with severe TBI, mean serum creatinine (0.94 mg/dL) was higher than in patients with moderate and mild TBI. The same occurred in patients whose outcome was death, in which the mean creatinine (1.13 mg/dL) was also higher than the patients who survived. When these data were adjusted, in the multivariate analysis for the variables gender, age group, etiology of TBI, severity of TBI, altered CT, neurosurgery and associated trauma, a strong association of serum creatinine dosage with death outcome was maintained (CR: 1.64; CI: 1.25-2.15). These data demonstrate the relevance of this research in the absence of similar analyses in the literature. Evaluating the accuracy of serum creatinine dosage as a prognosis of death outcome, the result is encouraging. It proved to be a test with satisfactory results (70%) since the area under the "ROC" curve was 67.2%. Seeking a cut-off point for this, the serum creatinine value of 1.18 mg/dL was the one that presented the best accuracy, presenting high specificity (89%), but low sensitivity (42%) for the death outcome.
CONCLUSIONS

The mean value of serum creatinine was higher in males, severe TBI, altered CT, DHS, brain swelling, pneumocephalus, and death outcome. It also had increasing values the higher the age range. In addition, it was independently associated with the death outcome. The serum creatinine value of 1.18 mg/dL represented the cut off point with the best specificity and sensitivity related to death.

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