Exploiting Machine Learning Technologies to Study the Compound Effects of Serum Creatinine and Electrolytes on the Risk of Acute Kidney Injury in Intensive Care Units

Hsin-Hung Liu  
Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University

Yu-Tseng Wang  
Graduate Institute of Networking and Multimedia, National Taiwan University

Meng-Han Yang  
Department of Computer Science and Information Engineering, National Kaohsiung University of Science and Technology

Wei-Shu Kevin Lin  (booklin2@gmail.com)  
Department of Emergency Medicine, National Taiwan University Hospital

Yen-Jen Oyang  
Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University

Research Article

Keywords: Acute kidney injury, Serum electrolyte, Intensive care unit, Machine learning

Posted Date: March 17th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2679715/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License

Additional Declarations: No competing interests reported.
Exploiting Machine Learning Technologies to Study the Compound Effects of Serum Creatinine and Electrolytes on the Risk of Acute Kidney Injury in Intensive Care Units

Hsin-Hung Liu¹, Yu-Tseng Wang ², Meng-Han Yang³, Wei-Shu Kevin Lin¹,4* and Yen-Jen Oyang¹,2,5*

¹Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei City, 10617, Taiwan (R.O.C.)
²Graduate Institute of Networking and Multimedia, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei City, 10617, Taiwan (R.O.C.)
³Department of Computer Science and Information Engineering, National Kaohsiung University of Science and Technology, No. 415, Jiangong, Kaohsiung City, 80761, Taiwan (R.O.C.)
⁴Department of Emergency Medicine, National Taiwan University Hospital, No. 7, Zhongshan S. Road, Taipei City, 10002, Taiwan (R.O.C.)
⁵Department of Computer Science and Information Engineering, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei City, 10617, Taiwan (R.O.C.)

*Corresponding authors. E-mails: booklin2@gmail.com (W.S K. Lin);
yjoyang@csie.ntu.edu.tw (Y.J. Oyang);
Contributing authors: qi3800@yahoo.com.tw (H.H. Liu); d05944001@ntu.edu.tw (Y.T. Wang); menghanyang@nkust.edu.tw (M.H. Yang);

Abstract
Assessing the risk of acute kidney injury (AKI) has been a challenging issue for clinicians in an intensive care unit (ICU) as AKI could lead to many complications and even fatality. However, several early signs of AKI are non-specific and the current clinical practice monitors only the level of serum creatinine and the volume of urine output. Therefore, it is of great medical merit to identify all possible risk factors of AKI. In recent years, a number of studies have reported the associations between several serum electrolytes and AKI. Nevertheless, the compound effects of serum creatinine, blood urea nitrogen (BUN), and clinically relevant serum electrolytes have not been comprehensively investigated. Accordingly, we initiated this study aiming to develop machine learning models that not only illustrate how these factors interact with each other but also provide new insights for developing new clinical practices to assess AKI risk. Our analyses reveal that among the factors investigated the levels of serum creatinine, chloride, and magnesium are the major risk factors associated with the development of AKI in ICUs.

Acknowledgments: The authors would like to acknowledge Dr. Albert Li for his professional comments and advice.

Keywords: Acute kidney injury, Serum electrolyte, Intensive care unit, Machine learning
Introduction

Acute kidney injury (AKI) frequently occurs, ranging from 20% to 50%, among the patients in an intensive care unit (ICU)\cite{1}. Since AKI could lead to many complications and even fatality, how to assess the risk of AKI is a critical issue for clinicians in an ICU\cite{2–4}. However, several early signs of AKI, including edema, hypertension, and oliguria, are non-specific. Therefore, the current practice monitors only the level of serum creatinine and the volume of urine output in order to assess the risk of AKI\cite{5, 6}.

Due to the observation above, scientists have been investigating the physiological signs that may be associated with the development of AKI. In recent years, a number of studies reported that the levels of several serum electrolytes, including chloride, phosphorus, magnesium, potassium, sodium, and calcium, were associated with the development of AKI\cite{7–9}. Suetrong et al. observed a linear correlation between the concentration of serum chloride and the development of AKI among sepsis/septic shock patients\cite{10}. Marttinen et al. reported a similar result and showed that the temporal chloride level was associated with an increased risk of AKI\cite{11}. The work by Moon et al. revealed that a high level of serum phosphorus increased the risk of AKI\cite{12}. Cheungpasitporn et al. showed that both hypomagnesemia and hypermagnesemia led to an increased risk of in-hospital acute renal failure\cite{13}. Thongprayoon et al. observed a U-shaped association between the level of serum ionized calcium and in-hospital AKI. Furthermore, both hypocalcemia and hypercalcemia were reported to be associated with an increased risk of hospital-acquired AKI\cite{14, 15} and Chen et al. discovered that abnormal levels of serum sodium or potassium before AKI diagnosis were more likely to lead to AKI progression and poor prognosis\cite{16}. Nevertheless, Yessayan et al. reported that the concentration of hyperchloremia and onset of AKI within 72 hours of admission were not correlated\cite{17}.

In addition to the studies addressed above, a latest trend is to exploit various machine learning algorithms, including artificial neural networks\cite{18}, support vector machines\cite{19}, Bayesian networks\cite{20}, and random forests (RF)\cite{21}, etc., to predict incidences of AKI and Song et al. reviewed how the conventional logistic regression (LR) and various machine learning methods performed in this respect\cite{22}. A representative study was conducted by Nenad Tomasev et al.\cite{23}. In their study, the authors employed the recurrent neural network to build their prediction models based on a cohort of 703,782 cases collected from the medical facilities of the U.S. department of veterans affairs.

Though the effects of several serum electrolytes on the development of AKI have been well reported, the compound effects of serum creatinine, blood urea nitrogen (BUN), and clinically relevant serum electrolytes have not been comprehensively investigated. Furthermore, the current clinical guidelines to assess the risk of AKI involve only the serum creatinine level and the volume of urine output. Therefore, it is of medical merit to develop a more comprehensive guideline that takes the compound effects of multiple serum electrolytes into consideration. In this study, we have exploited the decision tree (DT) models\cite{24–26} and the RF models\cite{27, 28} aiming not only to illustrate how these factors interact with each other but also to provide new insights for developing new clinical practices.

Methods

Study Cohort

Our study cohort was extracted from the Medical Information Mart for Intensive Care (MIMIC)-IV database, version 1.0, published in March 2021\cite{29, 30}. Fig. 1 shows the flow that we followed to generate our study cohort. Initially, the dataset contains 256,878 clinical records collected at the emergency department and the intensive care unit of Beth Israel Deaconess Medical Center between 2008 and 2019. Then, we followed the 2012 kidney disease: improving global outcomes (KDIGO) guideline to determine whether a patient suffered from AKI during his/her stay in the ICU\cite{33}. In this respect, a patient was labeled as suffering from AKI, if his/her serum creatinine level increased by 0.3 mg/dL within 48 hours or 1.5 times within 7 days. As the guideline requires two readings of the serum creatinine level, 205,482 records in the database were excluded due to a lack of required information and only 51,396 records were included for subsequent analyses. Since one patient could be admitted into the
Fig. 1: The flow for generating the study cohort

Criterion (1):
(i) For a patient who had suffered from AKI, we included only the record corresponding to his/her stay in the ICU during which the patient suffered from AKI the first time.
(ii) For a patient who had never suffered from AKI, we included only the record corresponding to his/her first stay in the ICU.

Criterion (2):
(i) The record of the case did not include all the readings listed in Table 2;
(ii) One or more readings in the record were within the highest 0.1% or the lowest 0.1% of the distributions;
(iii) One or more readings in the record were not measured within 168 hours from admission.

ICU more than once times, for a patient who had suffered from AKI, we included only the record corresponding to his/her stay in the ICU during which the patient suffered from AKI the first time. On the other hand, for a patient who had never suffered from AKI, we included only the record corresponding to his/her first stay in the ICU. As a result, only 41,878 cases remained. In the next step, we employed the criteria provided in Table 1 to exclude those patients whose medical records showed AKI related comorbidities[34] so that the interferences from other factors such as renal impairment, cardiac failure, diabetes, and electrolytes imbalances would be avoided. After this step, only 17,085 cases remained in the dataset. Finally, we employed the following excluding criterion to further screen the dataset:
(1) the record of the case did not include all the readings listed in Table 2;
(2) one or more readings in the record were within the highest 0.1% or the lowest 0.1% of the distributions;
Table 1: Excluding criteria for cases with AKI-related comorbidities/diseases

<table>
<thead>
<tr>
<th>Comorbidities/disease</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>403.11, 403.91, 404.12, 404.92, 584.5-584.9, 585.1-585.9, 586, V42.0, V45.1, V56.0, V56.8</td>
<td>I12.0, II13.1, N17.0-N17.2, N17.8, N17.9, N18.1-N18.9, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9</td>
<td>I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, 142.5-I42.9, I43, I50.0- I50.9, P29.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250.0-250.7, 250.9</td>
<td>E10.0-E10.9, E11.0-E11.9, E12.0-E12.9, E13.0-E13.9, E14.0-E14.9</td>
</tr>
<tr>
<td>Fluid and electrolyte disorders</td>
<td>276.0-276.9</td>
<td>E22.2, E86.0, E86.1, E86.9, E87.0-E87.8</td>
</tr>
</tbody>
</table>

1 Including end-stage renal disease, AKI and chronic kidney disease.

Table 2: Demographic analysis of the study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>550 cases with AKI (mean ± SD)</th>
<th>12,152 cases without AKI (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>65.68±14.69</td>
<td>60.34±17.67</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of male (%)</td>
<td>349 (63.45%)</td>
<td>6,757 (55.60%)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Number of female (%)</td>
<td>201 (36.55%)</td>
<td>5,395 (44.40%)</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>26.74±15.39</td>
<td>18.06±8.90</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.36±0.64</td>
<td>0.86±0.26</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>110.37±0.73</td>
<td>107.39±5.28</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.79±0.75</td>
<td>4.47±0.63</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>142.81±5.77</td>
<td>141.23±4.59</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>2.53±0.52</td>
<td>2.28±0.44</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.40±1.34</td>
<td>3.80±0.93</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Calcium non-ionized (mg/dL)</td>
<td>8.76±0.73</td>
<td>8.73±0.71</td>
<td>&lt;0.01**</td>
</tr>
</tbody>
</table>

SD: standard deviation.
The symbol ** indicates statistical significance.

For categorical variables, the p-values were calculated based on the χ² test[31, 32].
For continuous variables, the p-values were calculated based on the Kruskal–Wallis test[31, 32].
(3) one or more readings in the record were not made within 168 hours from admission.

In the end, our study cohort contained 550 AKI positive cases and 12,152 AKI negative cases. The demographic analysis of the study cohort is presented in Table 2.

**Machine Learning Models**

As mentioned earlier, we have resorted to the DT and the RF models in order to investigate the compound impacts of two or more factors and provide a manifest picture of how these factors interact with each other. In particular, we have focused on the compound effects of serum creatinine, BUN, and clinically relevant serum electrolytes. Table 2 lists the 10 variables incorporated to generate the prediction models.

In order to address the needs in different clinical scenarios, we generated prediction models with different levels of sensitivity and examined the prediction rules embedded in these models. In this respect, we set parameters of the machine learning packages to various combinations and employed the 5-fold cross-validation to evaluate the levels of sensitivity delivered by the prediction models generated with these alternative parameter settings. Then, we picked up the prediction models that delivered the desired levels of sensitivity. Supplementary Table 1 summarizes the software packages and parameter settings employed to generate the prediction models.

**Results**

Table 3 summarizes the performance of the DT, RF and LR models observed during the 5-fold cross-validation procedure. The performance of the LR models was included to provide a reference because LR models are widely employed in biomedical research communities. The detailed performance data is presented in Supplementary Table 2.

The performance data in Table 3 reveals that with respect to the relative risk and the AUC (area under the receiver operating characteristic curve), the DT model that delivered sensitivity at the level of 0.95 performed significantly superior to the RF model that delivered the same level of sensitivity. It is also observed that the RF model that delivered sensitivity at the level of 0.80 performed superior to the rival DT model in terms of the relative risk but performed inferior to the rival DT model in terms of the AUC. Since the overall performance of the DT models was marginally superior to that of the RF models, in the following discussions, we will focus on the DT models and the decision rules embedded in the models.

Fig. 2a and Fig. 2b show the DT models generated with the combinations of parameters cp and prior set to (0.005, 0.5835) and (0.01, 0.744), respectively. According to the 5-fold cross-validation addressed above, with cp and prior set to these two combinations, the DT models generated should deliver sensitivity at the levels of 0.80 and 0.95, respectively. One interesting observation regarding the DT model shown in Fig. 2a is that the model predicts a patient with a serum creatinine level higher than 1.25 mg/dL to be at high risk. This prediction rule comes very close to the serum creatinine level of 1.3 mg/dL commonly practiced by physicians to determine whether a patient is at high risk of progression to AKI. It is also observed that the DT model shown in Fig. 2b predicts a patient with a serum creatinine level higher than 0.95 mg/dL to be at high risk. This observation implies that 0.95 mg/dL can be employed as an alternative threshold, if the physician wants to increase the sensitivity of his/her medical judgment.

The DT model shown in Fig. 2a further reveals that for a patient with a serum creatinine level between 0.95–1.25 mg/dL his/her level of serum magnesium can be employed as a warning sign. If the reading is higher than 2.45 mg/dL, then the patient is at high risk. If not, we should further examine his/her level of serum chloride. If the patient’s level of serum chloride is over 106.5 mEq/L, then the patient is at high risk.

The blue polygon in Fig. 3 encircles the high-level structure shared by both DT models shown in Fig. 2. The common structure reveals that for a patient with a serum creatinine level between 0.75–0.95 mg/dL we should further examine his/her levels of serum magnesium and chloride. The patient is at high risk, if (1) his/her level of serum chloride is higher than 113.5 mEq/L; or
Table 3: Summary of the performance observed during the 5-fold cross-validation process

<table>
<thead>
<tr>
<th>Level of sensitivity</th>
<th>Model</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>AUC</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95</td>
<td>DT</td>
<td>0.949</td>
<td>0.479</td>
<td>0.076</td>
<td>0.767</td>
<td>16.893</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.949</td>
<td>0.382</td>
<td>0.065</td>
<td>0.666</td>
<td>13.012</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>0.949</td>
<td>0.414</td>
<td>0.068</td>
<td>0.855</td>
<td>13.872</td>
</tr>
<tr>
<td>0.80</td>
<td>DT</td>
<td>0.798</td>
<td>0.721</td>
<td>0.116</td>
<td>0.823</td>
<td>9.84</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.799</td>
<td>0.732</td>
<td>0.119</td>
<td>0.766</td>
<td>10.141</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>0.799</td>
<td>0.773</td>
<td>0.137</td>
<td>0.857</td>
<td>11.982</td>
</tr>
</tbody>
</table>

PPV: a positive predictive value, also known as precision
AUC: an area under the receiver operating characteristic curve

(2) his/her level of serum chloride is between 105.5-113.5 mEq/L and the level of serum magnesium is higher than 2.35 mg/dL.

In summary, the structures of the two DT models shown in Fig. 2 illustrate that the levels of serum creatinine, chloride, and magnesium are the 3 major factors associated with the development of AKI. Though the level of serum phosphorus is present in these DT models, the nodes corresponding to the level of serum phosphorus are located in the lower parts of the structures, which implies that these nodes play less significant roles in the decision rules.
Fig. 2: The DT models with two different levels of sensitivity

The prediction for a case is made by traversing the DT starting from the node at the top of the tree, the root node colored yellow. Then, the traverse precedes by following the branch originating from a node that matches the corresponding attribute value of the case. The traverse ends at one of the nodes at the bottom level of the tree. The “n+” and “n−” symbols in each node respectively denote the number of positive cases and the number of negative cases in the cohort that meet the criteria specified along the path from the root node to this particular node. If the traverse ends at a node colored red, then the prediction would be positive. On the other hand, if the traverse ends at a node colored green, then the prediction would be negative.
Fig. 3: The part encircled by the blue polygon is the common structure shared by the 2 DT models shown in Fig. 2.
Discussion

As of today, the clinical practice to assess the risk of AKI is based on the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury, which monitors only the level of serum creatinine and the volume of urine output. Therefore, identifying the risk factors of AKI and exploiting machine learning technologies to predict AKI incidences have attracted a lot of attention in biomedical research communities. In this respect, several serum electrolytes have been reported to be associated with the development of AKI. Nevertheless, the compound effects of serum creatinine, BUN, and clinically relevant serum electrolytes have not been thoroughly investigated. With this observation, we initiated this study aiming to not only illustrate how these factors interact with each other but also provide new insights for developing new clinical practices for assessing AKI risk.

We can summarize our analyses by identifying the levels of serum creatinine, chloride, and magnesium as the three major factors, among the 10 factors listed in Table 2, which are associated with the development of AKI. As the level of serum creatinine has been one of the major factors monitored in current clinical practice, our results suggest that the levels of serum chloride and magnesium should be taken into consideration in order to enhance the clinical guidelines.

There are several limitations with this study. Firstly, this is a retrospective study based on the data extracted from the MIMIC-IV database. Therefore, the results derived from this study should not be extensively applied in the decision process without taking into consideration the ethnic composition of the patients and the medical interventions that these patients may receive. Secondly, our study was based on the clinical records collected in ICUs. It implies that the patients involved were in serious health conditions. Furthermore, as the data in Table 2 shows, these patients were relatively old. Therefore, the results observed in our analyses should not be generalized to patients in different health conditions and different age groups. Thirdly, our results only illustrate the associations between the risk factors investigated and the incidences of AKI. In other words, causal inferences have yet to be studied.

Conclusion

This study has led to in-depth understanding about the compound effects of serum creatinine, chloride, and magnesium on the development of AKI in ICUs. The understanding provides the crucial clues not only for future enhancement of the clinical practices but also for future investigation of the physiological mechanisms involved.

Supplementary information.
Supplementary Table 1: Summary of the software packages employed and parameter ranges
Supplementary Table 2: The detailed performance data observed in the 5-fold cross-validation process

Declarations

Ethical Approval. Not applicable.
Competing interests. Not applicable.
Authors’ contributions. Hsin-Hung Liu initiated the study and all authors contributed to the development of the methods. Software development and data analyses were performed by Yu-Tseng Wang. Wei-Shu Kevin Lin and Yen-Jen Oyang supervised the study and wrote the first version of the manuscript. All authors commented on previous versions of the manuscript and approved the final manuscript.

Funding. This work was partially supported by National Taiwan University grant #FD107016.

References


Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SI1.pdf