

Development and Verification of a Time Series AI Model for Acute Kidney Injury Detection Based on a Multicenter Distributed Research Network

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Abstract

Background: Acute kidney injury (AKI) is a marker of clinical deterioration and renal toxicity.

While there are many studies offering prediction models for the early detection of AKI, those predicting AKI occurrence using distributed research network (DRN)-based time series data are rare.

Objective: In this study, we aimed to detect the early occurrence of AKI by applying the interpretable LSTM-based model on a hospital EHR-based time series in patients who took nephrotoxic drugs using a DRN.

Methods: We conducted a multi-institutional retrospective cohort study of data from six hospitals using a DRN. For each institution, a patient-based dataset was constructed using five drugs for AKI, and the interpretable multi-variable long short-term memory (IMV-LSTM) model was used for training. This study employed propensity score matching to mitigate differences in demographics and clinical characteristics. Additionally, the temporal attention values of the AKI prediction model's contribution variables were demonstrated for each institution and drug, with differences in highly important feature distributions between the case and control data confirmed using one-way analysis of variance.

Results: This study analyzed 8,643 and 31,012 patients with and without AKI, respectively, across six hospitals. When analyzing the distribution of AKI onset, vancomycin showed an earlier onset (median: 12 days), and acyclovir was the slowest compared to the other drugs (median: 23 days). Our temporal deep learning model for AKI prediction performed well for most drugs. Acyclovir had the highest average area under the receiver operating characteristic curve score per drug (0.94), followed by acetaminophen (0.93), vancomycin (0.92), naproxen (0.90), and celecoxib (0.80). Based on the temporal attention values of the variables in the AKI prediction model, verified lymphocytes and calcium had the highest attention, whereas lymphocytes, albumin, and hemoglobin tended to decrease over time, and urine pH and prothrombin time tended to increase.

Conclusions: Early surveillance of AKI outbreaks can be achieved by applying the IMV-LSTM based on time series data

through hospital electronic health records (EHR)-based DRNs. This approach can help identify risk factors and enable early detection of adverse drug reactions when prescribing drugs that cause renal toxicity before AKI occurs.

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Original Manuscript

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Original Paper

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Abstract

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In this study, we aimed to detect the early occurrence of AKI by applying the interpretable LSTM-based model on a hospital EHR-based time series in patients who took nephrotoxic drugs using a DRN.

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We conducted a multi-institutional retrospective cohort study of data from six hospitals using a DRN. For each institution, a patient-based dataset was constructed using five drugs for AKI, and the interpretable multi-variable long short-term memory (IMV-LSTM) model was used for training. This study employed propensity score matching to mitigate differences in demographics and clinical characteristics. Additionally, the temporal attention values of the AKI prediction model's contribution variables were demonstrated for each institution and drug, with differences in highly important feature distributions between the case and control data confirmed using one-way analysis of variance.

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This study analyzed 8,643 and 31,012 patients with and without AKI, respectively, across six hospitals. When analyzing the distribution of AKI onset, vancomycin showed an earlier onset (median: 12 days), and acyclovir was the slowest compared to the other drugs (median: 23 days). Our temporal deep learning model for AKI prediction performed well for most drugs. Acyclovir had the highest average area under the receiver operating characteristic curve score per drug (0.94), followed by acetaminophen (0.93), vancomycin (0.92), naproxen (0.90), and celecoxib (0.89). Based on the temporal attention values of the variables in the AKI prediction model, verified lymphocytes and calcium had the highest attention, whereas lymphocytes, albumin, and hemoglobin tended to decrease over time, and urine pH and prothrombin time tended to increase.

Conclusions:

Early surveillance of AKI outbreaks can be achieved by applying the IMV-LSTM based on time series data through hospital electronic health records (EHR)-based DRNs. This approach can help identify risk factors and enable early detection of adverse drug reactions when prescribing drugs that cause renal toxicity before AKI occurs.

Keywords: adverse drug reaction, real world data, multicenter study, distributed research network, common data model, time series AI



Introduction

Acute kidney injury (AKI) is associated with a mortality rate of 40%–70% in hospitalized patients who develop AKI and causes significant kidney damage even after recovery, leading to dialysis, longer hospital stays, and increased costs of care [1-4]. Early detection of AKI increases the likelihood of AKI prevention, associated morbidity, and costs [5]. As no specific treatment can reverse AKI and the recognition of patients at risk of AKI before diagnosis contributes to better clinical outcomes than treatment after AKI occurs [6], early detection of AKI is essential for prompt therapeutic intervention.

Several studies have attempted to predict AKI occurrence. With the increasing availability of clinical databases, models have been developed to predict the occurrence of AKI using electronic health records (EHRs) [7-18]. Although these studies used EHRs, the number of patients in the patient population was small because they focused on specific patients, such as surgical patients, patients with sepsis, and older adults. There have also been a number of studies using artificial intelligence (AI) models to predict AKI. Although attempts have been made to predict the occurrence of AKI early, few models have provided clear rationales and explanations [19-21]. Therefore, time series data analysis is required for AKI prediction models to reflect the temporal information between variables [22]. Time series analysis for AKI is necessary because the length of time for each patient stays in a hospital or intensive care unit can differ from person to person, and the frequency of measurements can vary from values that are measured continuously (e.g., blood pressure) to laboratory values that are measured on an as-needed basis. Recently, an Interpretable multi-variable long short-term memory (IMV-LSTM) method for considering time series data has been published [23]; however, little research has been conducted on this method.

To address these issues, this study aimed to apply and validate a multicenter-based explainable time series AI model for predicting the occurrence of AKI caused by specific nephrotoxic drugs in six hospitals in South Korea by utilizing a large clinical database using a common data model (CDM) through a distributed research network (DRN).

Methods

Study design

This retrospective observational cohort study analyzed the EHRs from six hospitals in South Korea

between 1994 and 2021 to predict AKI. The EHRs were converted to OMOP-CDM (Observational Medical Outcomes Partnership Common Data Model) version 5.3.1. The data sources of the six hospitals used are as follows: Severance Hospital (SH), Gangnam Severance Hospital (GSH), Konyang University Hospital (KYUH), Ajou University Hospital (AJUH), Seoul National University Cancer Hospital (SNUH), and the National Cancer Center (NCC). An overall diagram of cohort composition is provided in Figure 1.

In our cohorts, we adopted criteria based on Serum Creatinine (SCr) to define AKI by “Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines” and the previously defined AKI classification stages mapped in the “injury” category[24-26]. Thus, the criterion is an increase in the SCr to two times the baseline value. As an alternative to the baseline SCr levels, we defined the upper limit normal (ULN) value of SCr as 1.2 mg/dl [27].

The targeted drugs were selected from five medications associated with a high risk of AKI in the U.S. Food and Drug Administration (FDA) and previous studies: acetaminophen, vancomycin, two non-steroidal anti-inflammatory drugs (NSAIDs) of naproxen and celecoxib, and one antiviral drug of acyclovir [21, 22].

The inclusion criteria were as follows: 1) The target drugs were administered, 2) patients with a visit record of at least 30 days prior to the observation period, 3) patients who underwent at least two SCr tests during the pre-observation period (0–60 days before the study). The exclusion criteria were as follows: 1) patients whose SCr tests were at least once outside the ULN value in the pre-observation period. Participants were divided into case and control cohorts based on whether previously defined AKI criteria for 60 days after taking the first medicine. The observation period refers to the time range before and after the initial medication intake for each patient within the cohort. The cohort definitions created using ATLAS, a web-based tool developed by OHDSI, are available as JavaScript Object Notation (JSON) files on GitHub.

To adjust for differences between cases and controls to reduce the effect of confounding variables, we used propensity score matching (PSM). Covariates included were age, sex, and SCr value at baseline. We normalized the covariate by applying standard scaling to ensure consistent dimensions across variables. A propensity score for each patient was generated by logistic regression. Patients were matched in a 1:3 ratio using a K-Nearest Neighbor (K-NN) algorithm using the Python scikit-learn library.

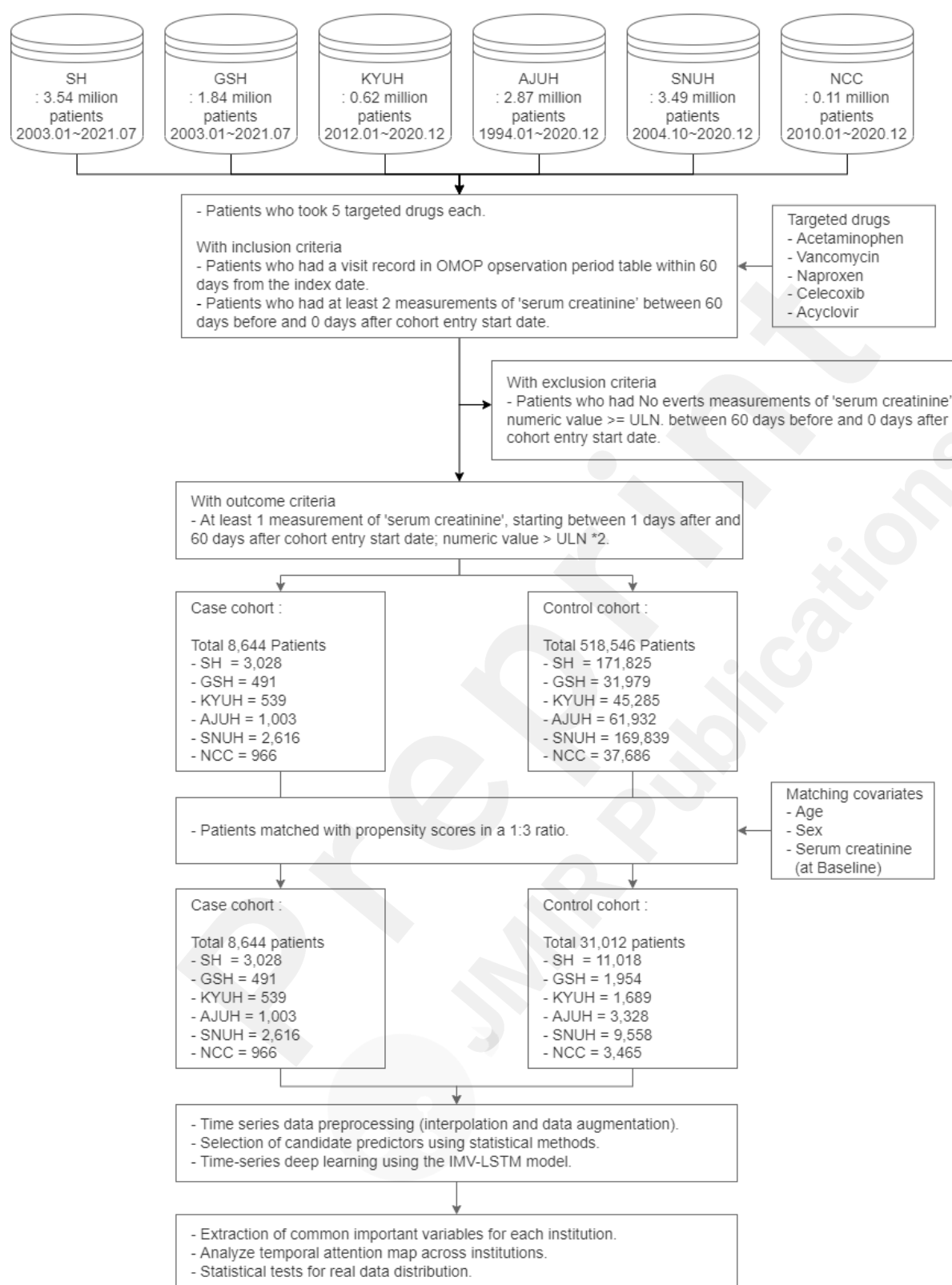


Figure 1.

The overall flowchart for predicting AKI events. SH: Severance Hospital; GSH: Gangnam Severance Hospital; KYUH: Konyang University Hospital; AJUH: Ajou University Hospital; SNUH: Seoul National University Cancer Hospital; NCC: National Cancer Center; ULN, Upper limit of normal; OMOP: Observational Medical Outcomes Partnership.

This study was approved by the Institutional Review Committee of Severance Hospital (approval number: 4-2021-1209), Gangnam Severance Hospital (approval number: 3-2021-0005), Konyang University Hospital (approval number: KYUH 2021-10-003-001), Ajou University Hospital (approval number: AJIRB-MED-MDB-21-676), Seoul National University Cancer Hospital (approval number: E-2207-151-1342), and the National Cancer Center (approval number: NCC2022-0184)

Candidate predictors for time series

Candidate predictors were extracted from several key domains within the CDM containing per-patient observational data, using structured query language tools in Python. Age and sex were used in the person domain, clinical laboratory tests in the measurement domain, medications in the drug exposure domain, diagnostic records in the condition occurrence domain, and surgical/procedure records in the procedure occurrence domain. Lab tests are treated as continuous variables, while other medications, conditions, procedures, etc. are treated as binary variables. Statistical methods were used to select the variables. To identify predictors, we tested the statistical significance of the difference between the enrollment time of the cohort and the onset date of AKI using the paired t-test and the McNemar test for continuous and dichotomous variables, respectively. To create a time series table, the candidate variables were pivoted into columns and dates were placed into rows. Missing values were handled in the following ways: forward fill for laboratory tests and diagnoses and zero fill for medications and treatments. The window size for predictions used four-week sequence data and was processed by shifting the data of the prediction cycle in two weeks.

AKI prediction modeling

LSTM models based on recurrence have been designed to process time series data [28]. Attention-based LSTM models were initially proposed for learning words and the relationships between words in natural language processing [29, 30] and later evolved into a key component of deep learning, becoming one of the methods used to provide interpretations, including importance scores for predicted outcomes.

As an advanced LSTM model, we used the IMV-LSTM module for the learning model, which is a multivariate LSTM neural network for the prediction and interpretation of multivariate time series [23]. This model improves on the LSTM-attention model, which can predict variable importance using multivariate inputs to configure variable-wise hidden states and mix both temporal and

variable levels of attention for improved interpretability. The model was trained for 200 epochs with a batch size of 64 and a learning rate of 1e-3. An Adam optimizer was used with early stopping after 20 epochs. The dataset was divided into training, test, and validation sets at 6:2:2 ratios. Prediction performance was evaluated using the area under the receiver operating characteristic curve (AUROC) value. Additionally, we used the accuracy, precision, F1 score, and area under the precision-recall curve (AUPRC) to ensure robustness for unbalanced data.

In this study, AKI prediction models were created for each hospital and drug. Each model had a different selection of candidate variables. To interpret the predictors in each model, variable- and temporal-wise attention scores were extracted from all trained models. These scores were then aggregated by calculating the overall temporal attention score, which was obtained by taking the weighted average of the temporal attention value over the attention value for each predictor variable. The resulting scores are plotted as heat maps for interpretation.

Statistical analysis

We used statistical packages based on Python and R for the statistical analysis. First, to compare the AKI and non-AKI groups, we calculated significance using the chi-square test for categorical variables and the two-sample t-test for continuous variables. Second, to identify differences in the pattern of AKI occurrence between cohorts and drugs, a histogram was plotted for patients in each cohort from the date of cohort entry (the first day of administration of the target drug) to the date of AKI occurrence. Differences between drugs were analyzed using an independent sample t-test. Third, we compared the distribution of the aggregated temporal attention scores with the actual trained data with box plots of the data for four weeks at one-week intervals. A repeated ANOVA test was performed to identify temporal differences.

Results

Demographic and Clinical Characteristics

The demographics of the 31,012 patients without AKI and the 8,643 patients with AKI across the six hospitals after PSM are shown in Table 1. By hospital, the cohort consisted of 14,046 patients from SH, 2,180 from GSH, 2,493 from KYUH, 4,331 from AJUH, 13,174 from SNUH, and 4,431 from NCC after matching the propensity scores. Propensity matching was performed using age, sex, and SCr levels at baseline. As for the changes in covariates, the difference in mean age decreased from 6.39 (60.65–54.26) to 0.44 (60.65–60.21), the difference in male ratio decreased from 16.49%

(63.17%– 46.68%) to 7.02% (63.17%– 56.15%), and the difference in SCr at baseline decreased from 0.14 (0.71–0.58) to 0.03 (0.71–0.67). (Supplementary Table 2). There were still statistically significant differences in PSM age (60.66 ± 15.86 vs. 60.22 ± 15.94 ; $P = 0.031$), gender (male: 63.17% vs. 56.15%; $P < .001$), and serum creatinine at baseline (0.71 ± 0.61 vs. 0.68 ± 0.41 ; $P < .001$). Patients who developed AKI had more severe neoplasms (active cancers) (70.6% vs. 44.26%, $P < .001$) and chronic liver disease (15.83% vs. 6.55%, $P < .001$). Moreover, the analysis revealed the following results: sepsis (6.5% vs. 1.94%; $P < .001$), diabetes mellitus (19.43% vs. 14.57%; $P < .001$), hypertension (27.81% vs. 23.5%; $P < .001$), anemia (9.81% vs. 4.8%; $P < .001$), and heart failure (4.79% vs. 3.07%; $P < .001$). and There was no significant difference between hypotension (0.24% vs. 0.21%; $P = 0.555$), potassium (4.11 ± 0.57 vs. 4.11 ± 0.51 ; $P = 0.477$), and renal artery stenosis (0.07% vs 0.03%; $P = 0.128$). Hypoalbuminemia, obesity, peripheral vascular disease, renal artery stenosis, liver dysfunction, and prior kidney surgery had low incidence rates ($< 2\%$). See Appendix 1 for the detailed cohorts for each drug and hospital.

	Case group							Control group							p-value
	SH (N=3,028)	GSH (N=491)	KYUH (N=539)	AJOU (N=1,003)	SNUH (N=2,616)	NCC (N=966)	Total (N=8,643)	SH (N=11,018)	GSH (N=1,689)	KYUH (N=1,954)	AJOU (N=3,328)	SNUH (N=9,558)	NCC (N=3,465)	Total (N=31,012)	
Age (mean ± SD)	61.83 ± 15.23	62.6 ± 15.04	67.91 ± 13.64	59.52 ± 15.79	57.89 ± 16.49	60.55 ± 12.24	60.65 ± 15.5	61.14 ± 15.37	62.26 ± 14.81	67.71 ± 13.55	59.67 ± 15.77	57.46 ± 16.61	60.14 ± 12.71	60.21 ± 15.61	0.02
Gender (n, %)															
Male	1,965 (64.89%)	286 (58.25%)	360 (66.79%)	628 (62.61%)	1652 (63.15%)	569 (58.9%)	5,460 (63.17%)	7,092 (64.37%)	985 (58.32%)	950 (48.62%)	1,765 (53.03%)	4,602 (48.15%)	2,018 (58.24%)	17,412 (56.15%)	<0.001
Female	1,063 (35.11%)	205 (41.75%)	179 (33.21%)	375 (37.39%)	964 (36.85%)	397 (41.1%)	3,183 (36.83%)	3,926 (35.63%)	704 (41.68%)	1,004 (51.38%)	1,563 (46.97%)	4,956 (51.85%)	1,447 (41.76%)	13,600 (43.85%)	<0.001
Sepsis	325 (10.73%)	50 (10.18%)	7 (1.3%)	139 (13.86%)	40 (1.53%)	1 (0.1%)	562 (6.5%)	373 (3.39%)	37 (2.19%)	21 (1.07%)	128 (3.85%)	41 (0.43%)	1 (0.03%)	601 (1.94%)	<0.001
Diabetes mellitus	915 (30.22%)	117 (23.83%)	65 (12.06%)	223 (22.23%)	300 (11.47%)	59 (6.11%)	1,679 (19.43%)	2,462 (22.35%)	266 (15.75%)	195 (9.98%)	593 (17.82%)	836 (8.75%)	167 (4.82%)	4,519 (14.57%)	<0.001
Chronic kidney disease	142 (4.69%)	3 (0.61%)	24 (4.45%)	13 (1.3%)	18 (0.69%)	2 (0.21%)	202 (2.34%)	271 (2.46%)	8 (0.47%)	51 (2.61%)	11 (0.33%)	40 (0.42%)	3 (0.09%)	384 (1.24%)	<0.001
Chronic liver disease	462 (15.26%)	56 (11.41%)	52 (9.65%)	139 (13.86%)	506 (19.34%)	16 (1.66%)	1,231 (14.24%)	766 (6.95%)	82 (4.85%)	71 (3.63%)	126 (3.79%)	759 (7.94%)	42 (1.21%)	1,846 (5.95%)	<0.001
Hypoalbuminemia	7 (0.23%)	2 (0.41%)	-	-	-	-	9 (0.1%)	9 (0.08%)	2 (0.12%)	-	-	-	-	11 (0.04%)	0.012
Hypotension	12 (0.4%)	4 (0.81%)	-	1 (0.1%)	4 (0.15%)	-	21 (0.24%)	30 (0.27%)	3 (0.18%)	-	4 (0.12%)	28 (0.29%)	-	65 (0.21%)	0.555
Hypertension	1,462 (48.28%)	179 (36.46%)	77 (14.29%)	351 (35.0%)	264 (10.09%)	71 (7.35%)	2,404 (27.81%)	4,178 (37.92%)	455 (26.94%)	360 (18.42%)	1,143 (34.34%)	924 (9.67%)	229 (6.61%)	7,289 (23.5%)	<0.001
Neoplasm (Active cancers)	2,112 (69.75%)	320 (65.17%)	255 (47.31%)	652 (65.0%)	2,081 (79.55%)	581 (60.14%)	6,001 (69.43%)	5,512 (50.03%)	531 (31.44%)	417 (21.34%)	1,282 (38.52%)	4,450 (46.56%)	2,470 (71.28%)	14,662 (47.28%)	<0.001
Heart failure	266 (8.78%)	13 (2.65%)	34 (6.31%)	33 (3.29%)	62 (2.37%)	6 (0.62%)	414 (4.79%)	629 (5.71%)	20 (1.18%)	105 (5.37%)	60 (1.8%)	127 (1.33%)	10 (0.29%)	951 (3.07%)	<0.001
Obesity	3 (0.1%)	2 (0.41%)	-	2 (0.2%)	3 (0.11%)	-	10 (0.12%)	36 (0.33%)	3 (0.18%)	4 (0.2%)	10 (0.3%)	50 (0.52%)	-	103 (0.33%)	<0.001
Peripheral vascular disease	25 (0.83%)	9 (1.83%)	19 (3.53%)	18 (1.79%)	10 (0.38%)	-	81 (0.94%)	51 (0.46%)	26 (1.54%)	69 (3.53%)	35 (1.05%)	37 (0.39%)	2 (0.06%)	220 (0.71%)	0.031

Liver dysfunction	62 (2.05%)	2 (0.41%)	2 (0.37%)	40 (3.99%)	31 (1.19%)	2 (0.21%)	139 (1.61%)	71 (0.64%)	4 (0.24%)	25 (1.28%)	46 (1.38%)	59 (0.62%)	3 (0.09%)	208 (0.67%)	<0.001
	541 (17.87%)	25 (5.09%)	35 (6.49%)	89 (8.87%)	154 (5.89%)	4 (0.41%)	848 (9.81%)	903 (8.2%)	53 (3.14%)	68 (3.48%)	176 (5.29%)	282 (2.95%)	7 (0.2%)	1,489 (4.8%)	<0.001
Prior kidney surgery	-	-	1 (0.19%)	3 (0.3%)	14 (0.54%)	-	18 (0.21%)	-	-	-	-	11 (0.12%)	1 (0.03%)	12 (0.04%)	<0.001
Laboratory test [before medication]															
Serum creatinine	0.46 ± 0.74	0.79 ± 0.23	0.99 ± 0.37	0.87 ± 0.37	0.87 ± 0.47	1.01 ± 0.29	0.75 ± 0.59	0.44 ± 0.51	0.76 ± 0.19	0.98 ± 0.22	0.84 ± 0.2	0.83 ± 0.18	0.98 ± 0.16	0.72 ± 0.4	<0.001
Glucose	126.89 ± 58.33	132.1 ± 52.11	150.75 ± 82.36	187.0 ± 23.0	121.48 ± 48.26	125.85 ± 50.05	126.93 ± 56.28	121.72 ± 55.7	124.3 ± 49.43	140.11 ± 78.81	151.5 ± 39.5	115.65 ± 40.5	120.88 ± 46.23	120.95 ± 51.85	<0.001
Potassium	3.92 ± 0.6	4.21 ± 0.47	4.14 ± 0.6	4.17 ± 0.55	4.22 ± 0.5	4.29 ± 0.56	4.11 ± 0.57	3.93 ± 0.55	4.22 ± 0.4	4.09 ± 0.54	4.15 ± 0.46	4.22 ± 0.43	4.28 ± 0.52	4.11 ± 0.51	0.477
Sodium	138.6 ± 4.16	137.27 ± 4.36	136.49 ± 4.61	138.48 ± 4.23	138.46 ± 3.96	138.31 ± 3.67	138.3 ± 4.14	139.44 ± 3.75	138.31 ± 3.58	137.74 ± 3.73	139.27 ± 3.85	139.71 ± 3.23	138.96 ± 3.37	139.28 ± 3.6	<0.001
BUN (Blood Urea Nitrogen)	17.83 ± 9.66	15.44 ± 6.58	17.67 ± 8.87	14.68 ± 6.36	14.72 ± 7.61	15.55 ± 6.13	16.13 ± 8.28	16.82 ± 7.48	15.78 ± 5.86	17.19 ± 7.62	14.9 ± 6.41	14.67 ± 5.14	14.63 ± 4.96	15.67 ± 6.47	<0.001

Table 1. Demonstration and clinical characteristics of Non-AKI and AKI patients across six hospitals after PSM. The p-value was obtained by conducting a two-sample t-test to compare the means of Case and Control.

Distribution of adverse drug events

To analyze the differences in drug patterns at the time of AKI occurrence, we assessed the pattern for each drug. The median number of days for the occurrence of AKI among the drug and cohort patients in the entire hospital was 17. Vancomycin appeared after a median period of 12 d, followed by naproxen (18 d), acetaminophen (19 d), celecoxib (22 d), and acyclovir (23 d). When comparing the IQR values, celecoxib (10–41 days) and Acyclovir (10–41 days) showed a relatively broad distribution, whereas acetaminophen (9–34 days) and naproxen (8–34 days) were distributed over 25 days. Vancomycin (5–25 days) exhibited the narrowest distribution. Compared to acetaminophen, vancomycin, and naproxen, celecoxib and acyclovir tended to be relatively distributed. We compared the onset times of all drug pairs and hospital pairs to check the similarity in AKI occurrence (see Figure 3). The pattern between specific

drugs was similar between celecoxib and acyclovir ($P=0.881$) and between acetaminophen and naproxen ($P=0.570$). The pattern between hospitals were similar for SH and AJUH ($P=0.984$), SH and GSH ($P=0.362$), GSH and AJUH ($P=0.415$), GSH and NCC ($P=0.238$), and SNUH and NCC ($P=0.263$).

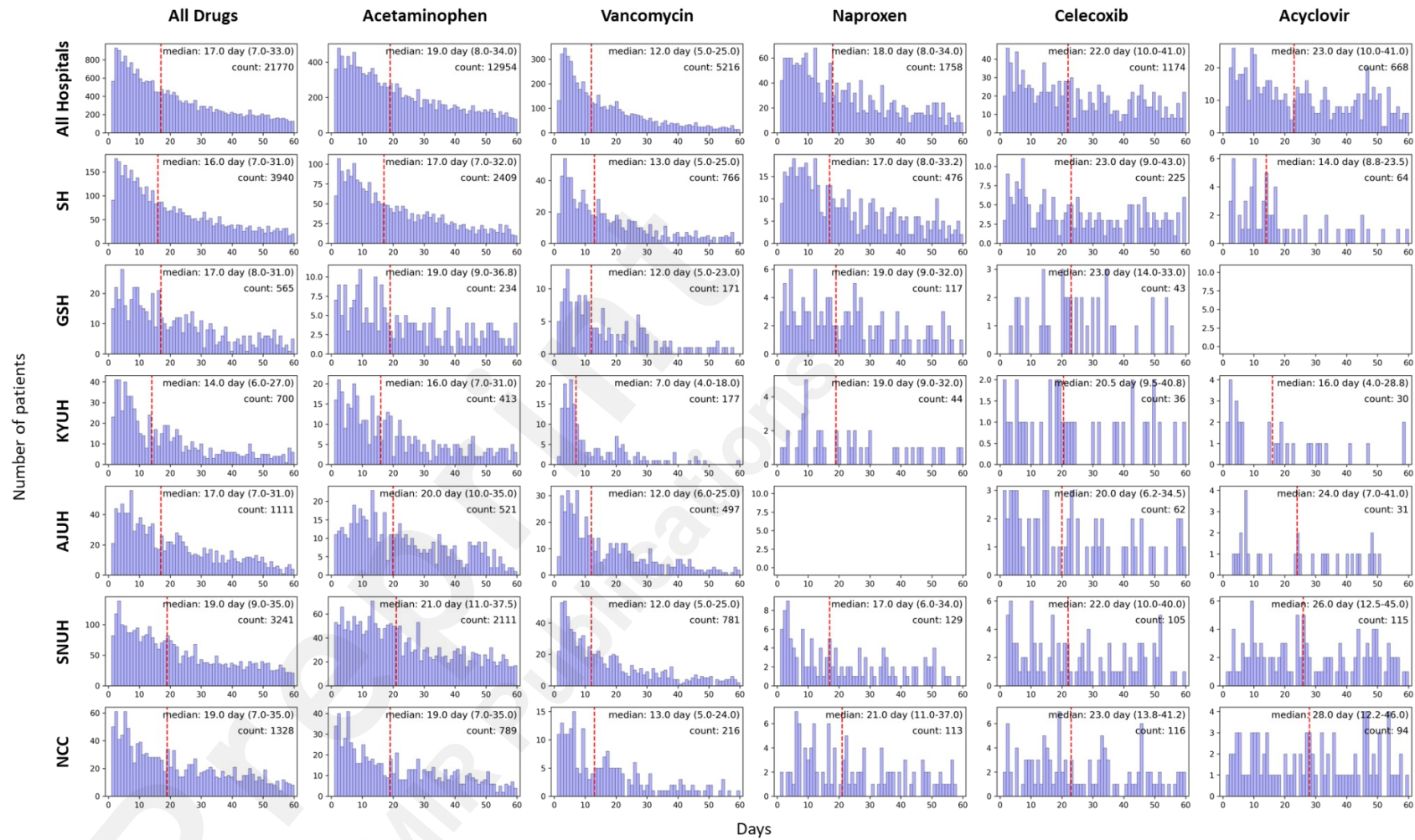


Figure 2. AKI onset time after drug administration at various medical centers. The red line shows the median value. AJUH's Naproxen and GSH's Acyclovir were excluded as the number of AKI case groups was less than 20.

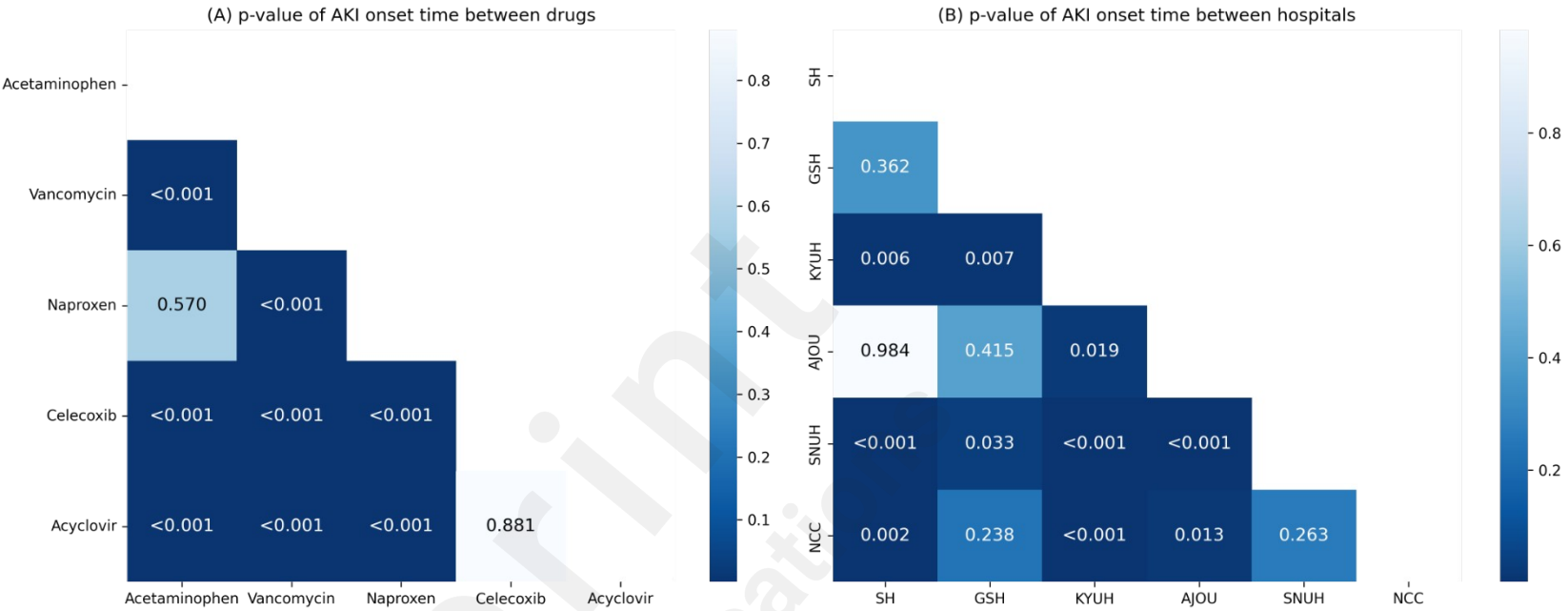


Figure 3. (A) Comparison of AKI onset time between drugs and (B) AKI onset time between hospitals. The p-value was obtained by conducting independent t-tests between each aggregated pair.

AKI prediction model performance

The AUROC for each drug and hospital to evaluate the AKI predictive model, based on respective test sets (internal validation) is shown in Figure 4. A total of 26 trained models achieved a high AUROC value of 0.92 on average with each verification dataset. In addition, among the average of the drugs, acyclovir had the highest average AUROC score of 0.94, followed by acetaminophen (0.93), vancomycin (0.92), naproxen (0.90), and celecoxib (0.89). The highest AUROC value (0.97) was observed for the model of SH's celecoxib, acyclovir, SNUH's vancomycin, and KYUH's acyclovir prescription patients.

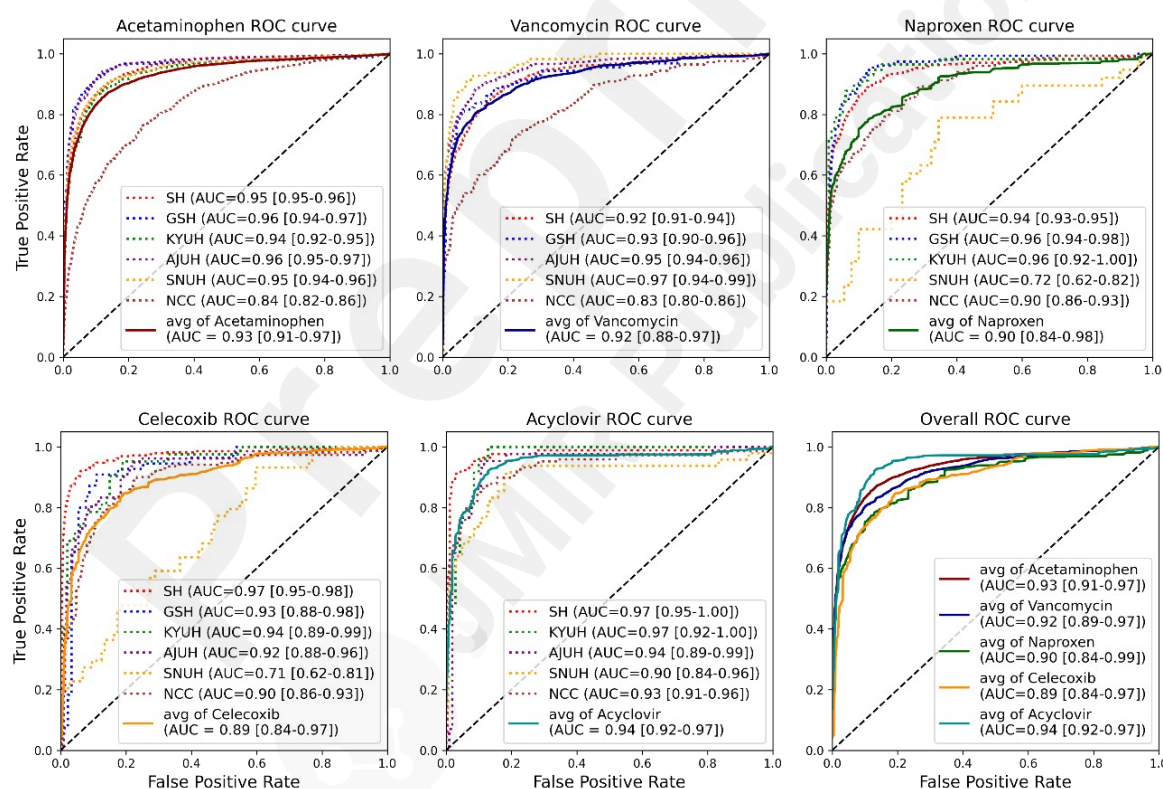


Figure 4. Receiver operating characteristic (ROC) curves of the AKI prediction model for each hospital and each drug. the square brackets indicate the 95% confidence interval (CI).

Appendix 2 presents data on the precision, accuracy, F1 score, and AUPRC of each predictive model. Overall, the average accuracy of the AKI prediction models was 0.88, whereas the average AUPRC and F1 scores were 0.78 respectively. The acyclovir

prescription model achieved the highest accuracy score (ACC: 0.91), followed by vancomycin (ACC: 0.90), acetaminophen (ACC: 0.89), naproxen (ACC: 0.89), and celecoxib (ACC: 0.86). Individually, the acyclovir-SH model showed the best performance with an AUPRC of 0.92 and an accuracy of 0.91.

Temporal feature importance of the AKI prediction model

To interpret the AKI prediction model, we demonstrated the temporal attention values of each contributing variable in the 4 weeks prior to AKI onset, which were weighted aggregates from the model for each drug and hospital, as shown in Figure 5-(A). The temporal change pattern of the actual data corresponding to each variable in the 4 weeks prior to AKI onset is shown in Figure 5-(B). We also confirmed the difference in the distribution of highly important features between the case and control data using one-way analysis of variance (ANOVA).

The last week of lymphocytes (attention score at -1 week: 0.41) and the second week of calcium (attention score at -3 weeks: 0.41) showed the highest attention scores, followed by albumin (attention score at -1 weeks: 0.37, attention score at -4 weeks: 0.37), hemoglobin (attention score at -4 weeks: 0.37), and cholesterol (attention score at -4 weeks: 0.37). In Figure 5-(A), the distribution of data by variable between the two groups was confirmed using actual data. There was a difference in data distribution between the case and control groups from the beginning. The values of lymphocytes, albumin, and hemoglobin in the case group decreased over time, while urine pH and prothrombin time in the case group tended to increase over time.

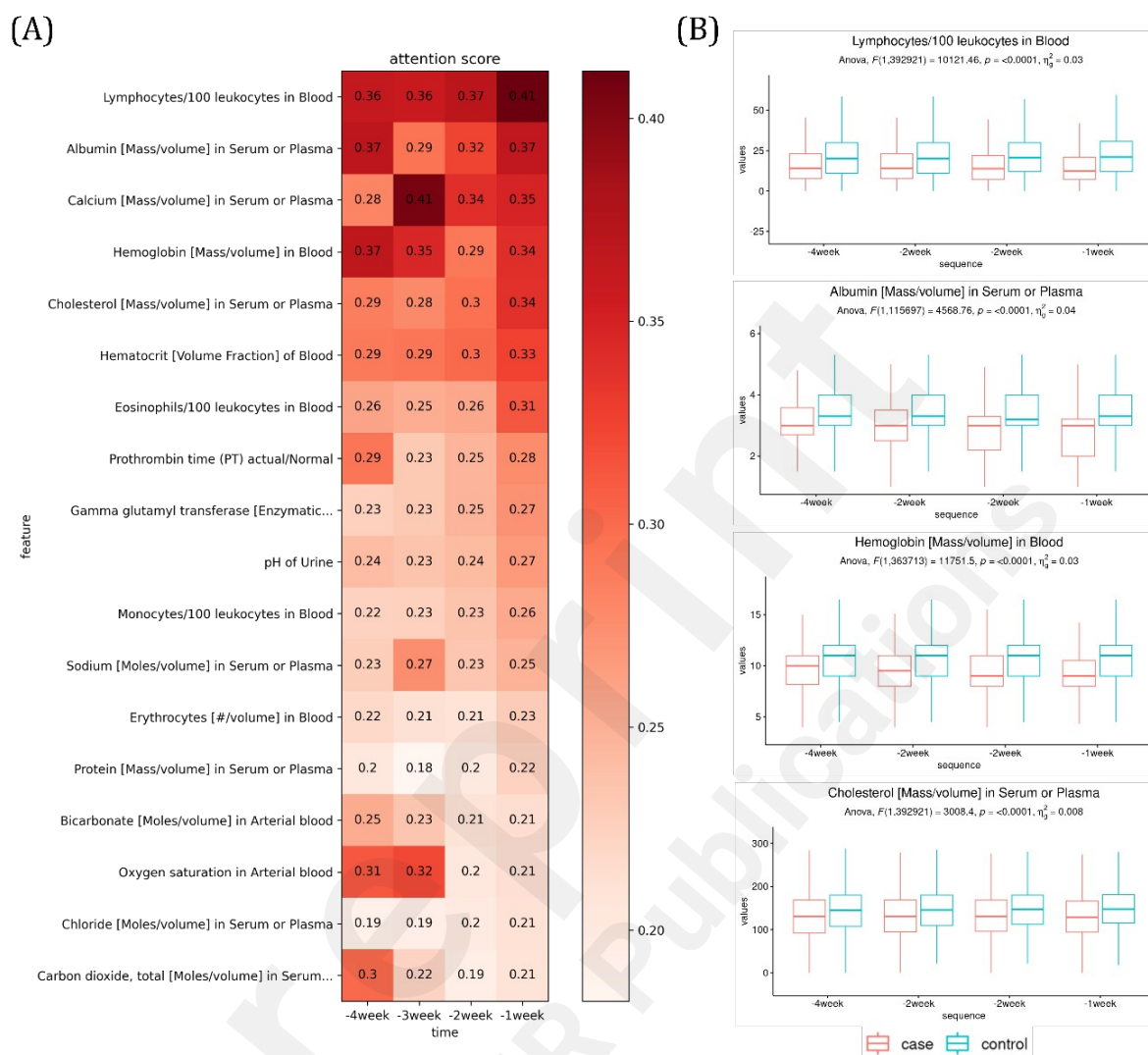


Figure 5. (A) Temporal attention score of important features of AKI prediction model and (B) distribution of data over time (p-value: Repeated measures ANOVA test). It shows the change over a four-week period prior to the AKI event.

Discussion

In this study, we developed time series-based IMV-LSTM models to predict AKI in patients taking specific nephrotoxic drugs using CDM-based DRNs in a six-hospital EHR-based system. The principal findings are as follows: First, this study provides an interpretation of the temporal importance of variables for predicting AKI, and the models also achieved high performance, with an average AUC of 0.92%. Secondly, our study is a

scalable multicenter study utilizing DRN, which can contribute to understanding drug-induced AKI. To the best of our knowledge, this is the first study that an AKI prediction model has been built by applying a time series-based IMV-LSTM model to CDM using EHR data from six hospitals.

We established a retrospective cohort of patients who took nephrotoxicity-inducing drugs at six hospitals. With respect to demographic characteristics, there were observed variations in the overall patient count and prevalence of comorbidities when comparing individuals with AKI and Non-AKI across different hospitals. Nevertheless, the majority of patients who developed AKI at most hospitals were older than 60 years of age and had a high prevalence of comorbidities, including cancer (69%), hypertension (28%), diabetes (19%), and chronic liver disease (14%), which is consistent with findings reported in previous studies [31-34].

The pattern of each drug's association with AKI (see Figure 2) showed that the median number of days for AKI onset when using nephrotoxic drugs was 17 days. The onset occurred earliest with vancomycin (12 days) and latest with acyclovir (23 days). In previous studies [35, 36], the time to onset of vancomycin-induced AKI showed a similar pattern to our results. We also found differences in the AKI onset between different classes within the same NSAID, and the multicenter AKI cohort showed similarities between hospitals. The finding of similar patterns in the AKI onset in the multicenter cohort supports the reliability of the AKI cohort and increases the explanatory power of AKI prediction models.

AKI is common among inpatients [37, 38]. Previous models predict AKI in ICU and surgical patients during hospital admission. For example, Zimmerman et al. predicted the occurrence of AKI in ICU inpatients (AUC: 0.783) [39], and Tseng et al. developed a predictive score for the development of AKI after cardiac surgery (AUC: 0.839) [40]. Hsu, Chien-Ning, et al. developed a risk score function for community-acquired acute kidney injury for inpatients (AUC:0.818) [41]. Koyner et al. developed a model to predict AKI in hospitalized patients (AUC:0.90) [10]. Despite this progress, few studies have applied time series deep learning to provide a temporal interpretation of drug-induced

AKI, and Our model stands out because it can predict nephrotoxic drug-induced AKI in a diverse hospital population.

This study achieved improved performance compared to previous AKI studies utilizing RNNs [21, 42-44]. Our model improves performance up to an AUC of 0.97 and an overall average of 0.92 which outperforms previous studies showing AKI prediction with RNN-based methods by Kim et al. in hospitalized patients (AUC: 0.927) [42], Rank, Nina et al. in cardiac surgery patients (AUC: 0.893) [44], and Xu, Jie et al. in inpatients (AUC: 0.908) [43]. These results show promise for our model as a tool to predict AKI and facilitate early intervention and mitigation strategies for patients.

This study also provides additional interpretations regarding the temporal importance of features for AKI prediction. Some studies need report information on interpretability or provide information about the interpretability of variables at the feature importance level [45]. However, our results show the importance of variables and the temporal importance of variables in the development of AKI. In this study, we highlight the vital role of temporal patterns of various indicators, such as lymphocytes, calcium, albumin, hemoglobin, and cholesterol, in predicting disease states, particularly the onset of AKI. The temporal pattern of lymphocytes increased gradually, peaking 1 week before AKI onset. The use of lymphocyte and neutrophil counts as predictive factors for AKI is consistent with other studies [46, 47]. Calcium shows a pattern of peaking 3 weeks before AKI onset, and Prior studies showed an association between impacted calcium metabolism and AKI[48, 49]. Albumin shows the highest pattern 1 and 4 weeks before onset, and low serum albumin levels (hypoalbuminemia) are a predictor of AKI [47, 50, 51]. Hemoglobin shows a pattern with a peak 4 weeks before onset, and previous studies have shown that the risk of AKI increases stepwise with a further decrease in hemoglobin concentration [52]. Temporal variations in variables based on reported laboratory data for the early detection of AKI emphasize the importance of monitoring and early intervention in populations.

In addition, this retrospective study can be conducted by a subsequent study to validate

the practicality of the AKI prediction model in clinical practice by it to a prediction system in a hospital EHR.

Limitations

This study has several limitations. First, because we used the CDM, it does not reflect the full range of clinical data. For example, we couldn't include admission records, which would have revealed the patient's condition. However, the use of CDM data allowed for a multicenter study and could be easily extended to other institutions that have converted to the CDM. Second, this was a retrospective study and could not address the underlying causes of AKI. Therefore, prospective studies are needed for validation with actual clinical data. Third, as with all retrospective studies, there may be unintentional patient selection bias and unaccounted for confounders. However, to compensate for these limitations, we tried to equalize the distribution of patient characteristics through PSM. We also used a limited follow-up period to minimize the impact of these factors.

Conclusions

This study demonstrates the high performance of the IMV-LSTM method for AKI prediction using hospital EHR-based time series data. Our model can provide real-time assessment of AKI occurrence and individualized risk factors for AKI using time series data. We also demonstrated the robustness of our model through multicenter validation using a common data model through a distributed research network of six hospitals in South Korea, which also proves that scalability to other institutions that are converted to the CDM is possible. This may provide an objective quantitative tool for identifying patients at risk of developing AKI.

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Conflicts of Interest

The authors declare no conflicts of interest.

Additional Information

The code for this study is available at GitHub [53].

Multimedia Appendix 1

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Abbreviations

ACC: Accuracy

ADR: Adverse Drug Reaction

AI: Artificial Intelligence

AJUH: Ajou University Hospital

AKI: Acute kidney injury

ANOVA: Analysis of variance

AUROC: Area Under the Receiver Operating Characteristic Curve

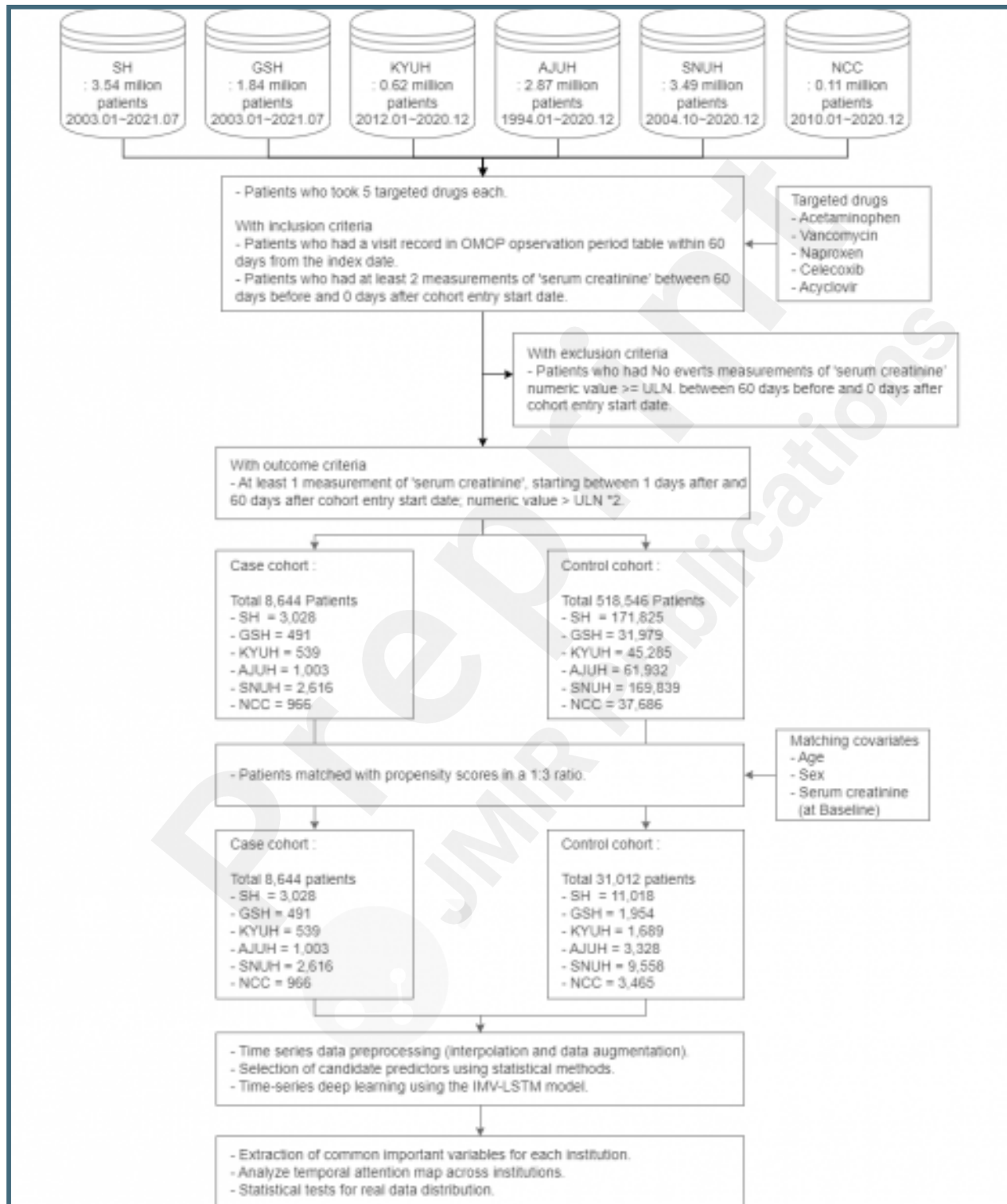
AUPRC: Area Under the Precision-Recall Curve

CDM: Common Data Model
DRN: Distributed Research Network
EHR: Electronic Health Records
FDA: Food and Drug Administration
GSH: Gangnam Severance Hospital
ICU: Intensive Care Unit
IMV-LSTM: Interpretable Multi-Variable Long Short-Term Memory
JSON: Java Script Open Notation
KDIGO: Kidney Disease Improving Global Outcomes
KYUH: Konyang University Hospital
MIMIC: Medical Information Mart for Intensive Care
NCC: National Cancer Center
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
OHDSI: Observational Health Data Sciences and Informatics
OMOP: Observational Medical Outcomes Partnership
PSM: propensity score matching
SCr: Serum Creatinine
SH: Severance Hospital
SNUH: Seoul National University Cancer Hospital
ULN: Upper limit of normal value

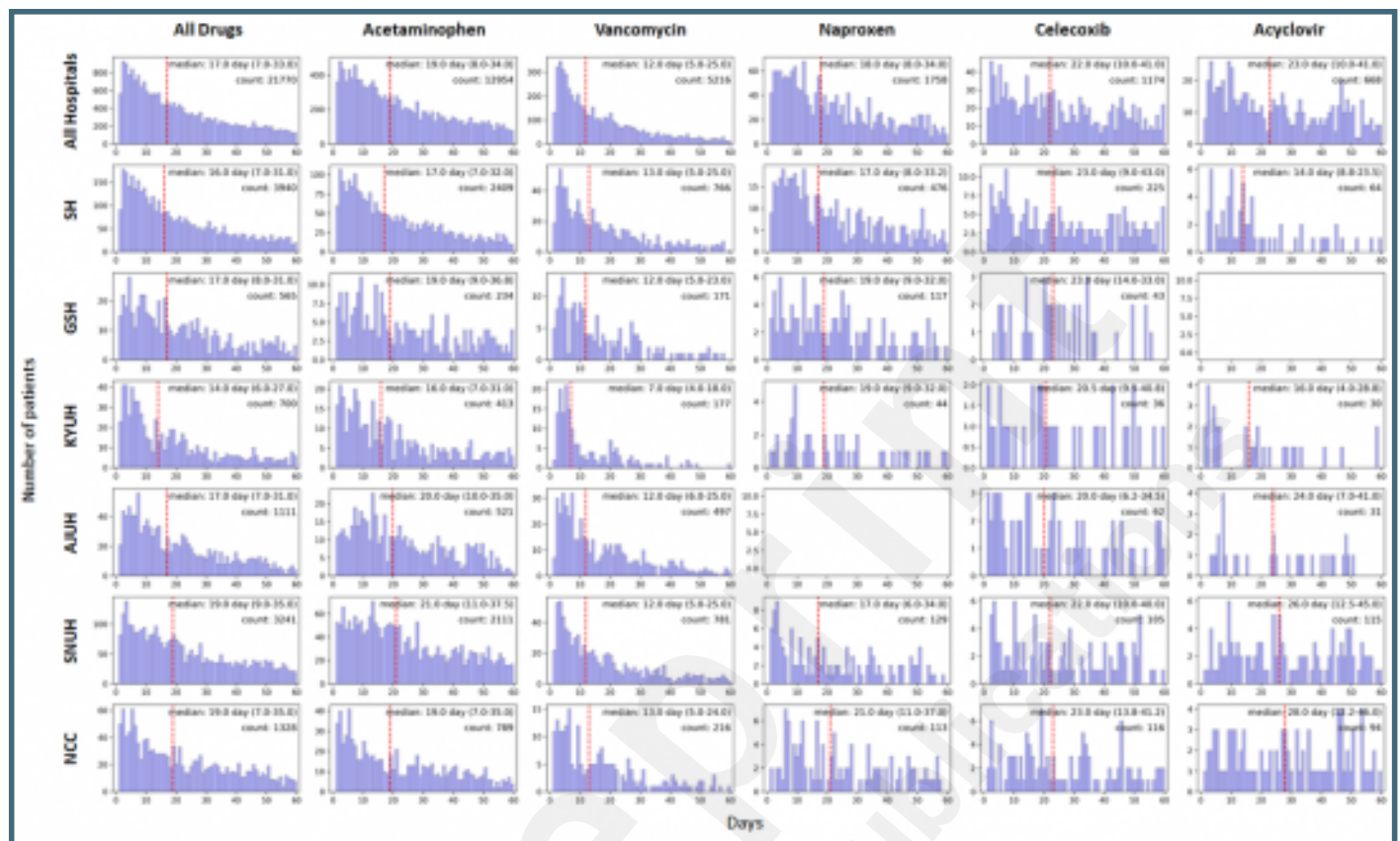
Supplementary Files

Figures

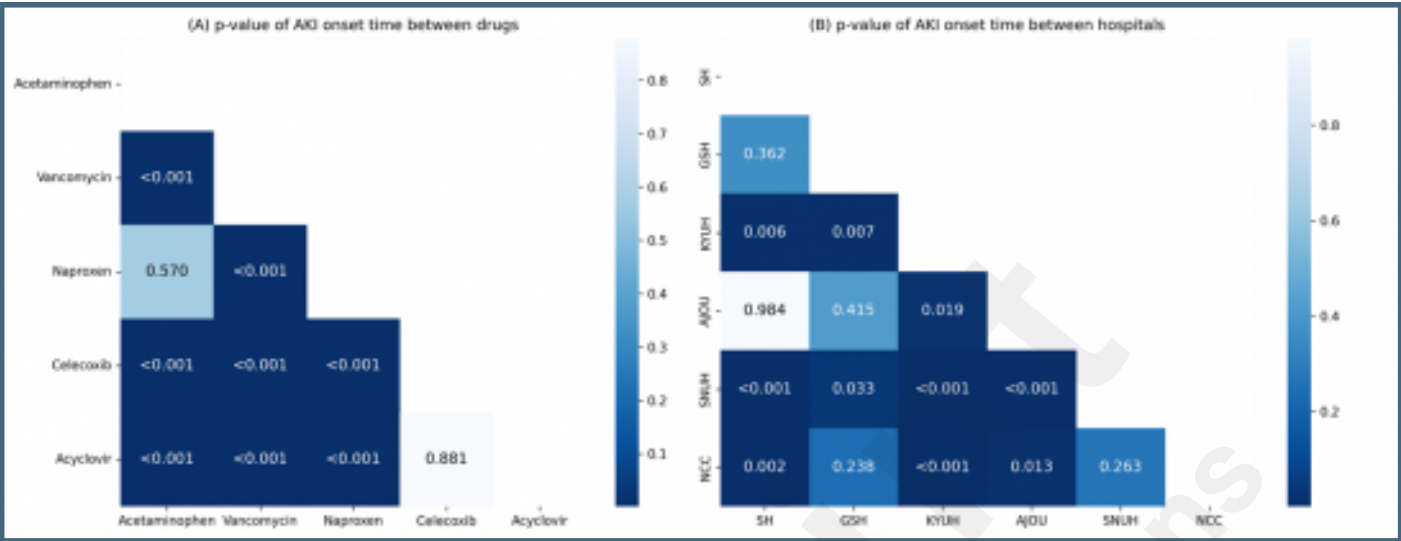
The overall flowchart for predicting AKI events. SH: Severance Hospital; GSH: Gangnam Severance Hospital; KYUH: Konyang University Hospital; AJUH: Ajou University Hospital; SNUH: Seoul National University Cancer Hospital; NCC: National Cancer Center; ULN, Upper limit of normal; OMOP: Observational Medical Outcomes Partnership.



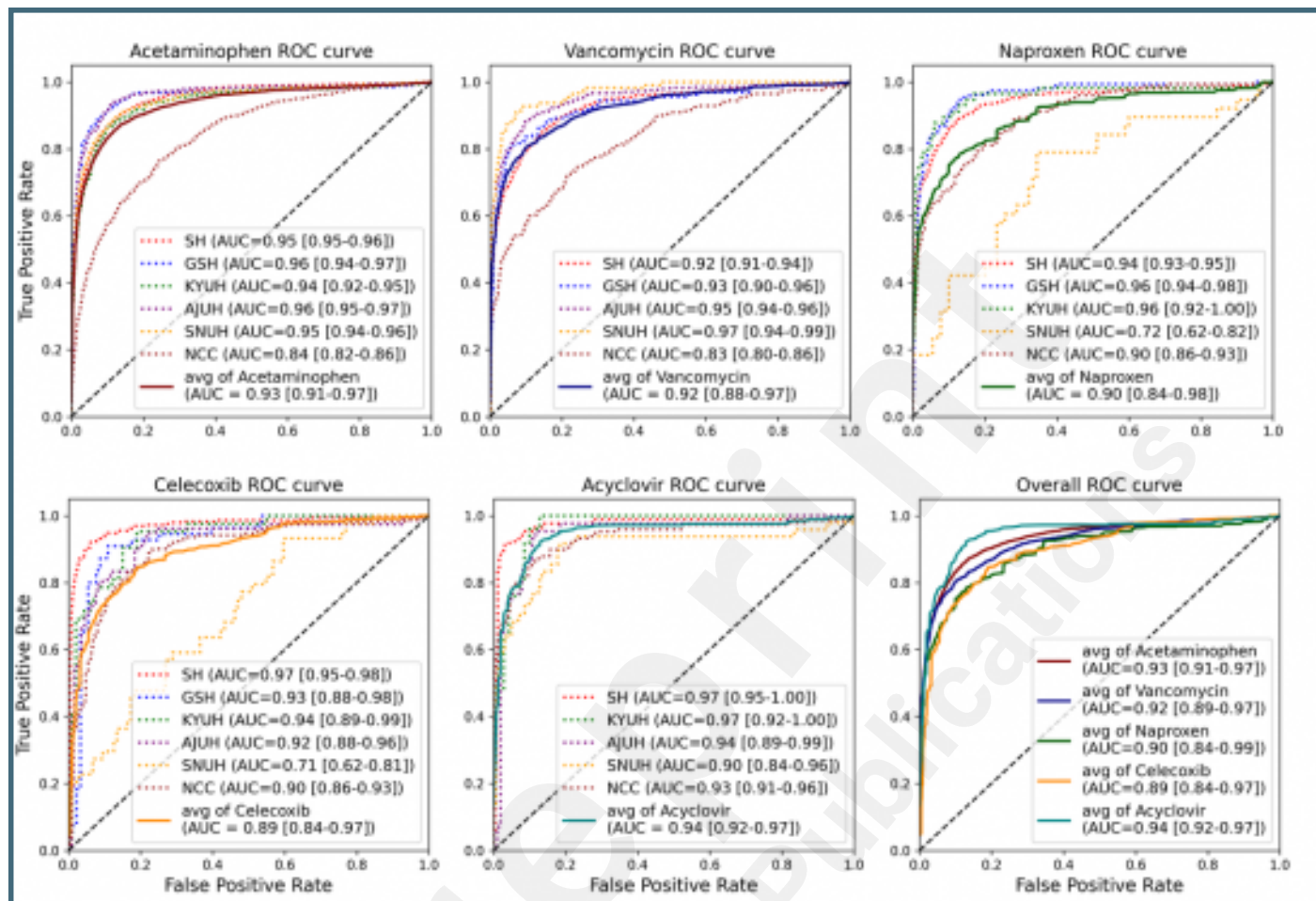
AKI onset time after drug administration at various medical centers. The red line shows the median value. AJUH's Naproxen and GSH's Acyclovir were excluded as the number of AKI case groups was less than 20.



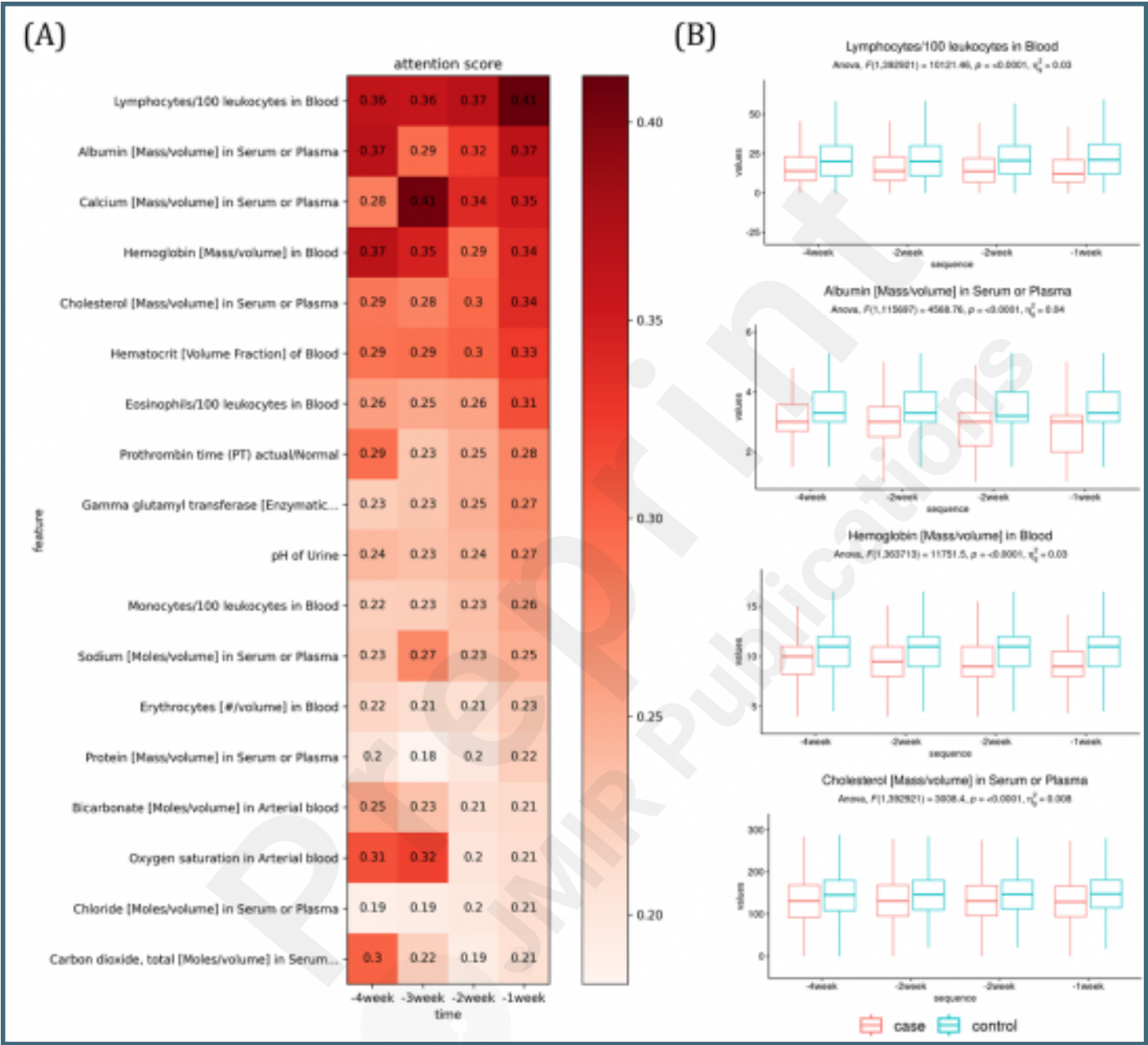
(A) Comparison of AKI onset time between drugs and (B) AKI onset time between hospitals. The p-value was obtained by conducting independent t-tests between each aggregated pair.



Receiver operating characteristic (ROC) curves of the AKI prediction model for each hospital and each drug, the square brackets indicate the 95% confidence interval (CI).



(A) Temporal attention score of important features of AKI prediction model and (B) distribution of data over time (p-value: Repeated measures ANOVA test). It shows the change over a four-week period prior to the AKI event.



Multimedia Appendixes

Study design.

URL: <http://asset.jmir.pub/assets/8d1bf9ea76c610b12665de1005d69134.xlsx>

Demographics for each institution.

URL: <http://asset.jmir.pub/assets/99f24e0931dfe55bec0ad33340a192dd.xlsx>

Feature Importance.

URL: <http://asset.jmir.pub/assets/e0e2267224e539061b2360a945ae0109.xlsx>

Model_performance.

URL: <http://asset.jmir.pub/assets/5bf78ad7c881cc6cfa65ef39e1d4112c.xlsx>

