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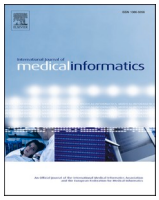

Characterizing the temporal changes in association between modifiable risk factors and acute kidney injury with multi-view analysis

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ABSTRACT

Background: Acute kidney injury (AKI) is a common life-threatening clinical syndrome in hospitalized patients. Advances in machine learning has demonstrated success in AKI risk prediction using electronic health records (EHRs). However, to prevent AKI, it is critical to identify clinically modifiable factors and understand their impact at different prevention windows.

Method: We extracted 4129 clinical variables including demographics, social history, past diagnoses, procedures, labs, medications, vitals from EHRs for a cohort of 144,084 eligible inpatient encounters. We developed a multi-view learning framework for XGBoost (MV-XGB) to enhance algorithm attention on modifiable factors. To study effects of modifiable factors at different time points, we built AKI prediction models at 24-hours, 48-hours, 72-hours before AKI onset. To characterize the temporal changes in effect of modifiable factors on AKI, we derived two indicators, inter-class score-difference and exposed-score-difference, based on SHAP values to compare effects of modifiable factors in different windows.

Result: MV-XGB effectively increased attention on modifiable factors (explained 92.4%-94.1% inter-class score-difference, i.e., predictive difference between AKI and non-AKI samples) while maintaining good predictive performance (AUROCs were 0.854, 0.798, 0.765 in models for 24–48-72 h AKI prediction respectively). We observed that 62% of predicted odds-ratio difference between AKI and non-AKI patients in 24 h can be explained by factors occurring between 24 and 72 h. Among the important modifiable factors, electrolyte balance explained 38.3% of the inter-class score difference increase between 24 h and 72 h, followed by high-risk medications (13.7%), care strategy (12.1%), blood pressure (10%), infection (7.8%), and anemia (5.4%). Effects of cardiac surgery or condition, respiratory ventilation, and anemia remained important longer than 72 h.

Conclusion: Better understanding of the clinically modifiable factors is important to AKI prevention. The proposed multi-view learning approach improved the identification of modifiable factors of AKI and allowed characterization of the temporal dynamics of their potential benefit in intervention.

1. Introduction

Acute kidney injury (AKI) is a life-threatening syndrome prevalent in hospitalized patients [1], affecting 10%-15% inpatients in general wards and > 50% in intensive care units, and its mortality is 20%-50% across patient populations [2,3]. AKI has many risk factors and their interactions make it difficult to forecast risk in real-time [4,5]. Artificial intelligence, powered by advances in machine learning, has made substantial progress across areas of medicine including AKI prediction [6–9].

Risk prediction using electronic health record (EHR) is important, but not the ultimate goal. According to reviews on AKI prevention, lack of reliable means for renal protection is still a challenge, and limitations exist in the timely and accurate risk identification, ideal timing of intervention, and variable effect of intervention in heterogeneous inpatients [10–14]. Most evidence on AKI prevention were generated from

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randomized controlled trials (RCT), but these trials only determined if an intervention is effective rather than which intervention is more important. To enhance AKI prevention, it is critical to identify the clinically modifiable risk determinants and understand their impact at different time intervals prior to disease onset [10,12].

EHR analysis is challenging because of its high-dimensional and heterogeneous nature; for example, a patient can be represented by different views: physiology status, exposures, and susceptibility. Factors in some of the views are clinically modifiable and some are not. Traditional analytical approach either combines all views in learning [6,9] or model individual views separately [15,16]. Learning from individual views (e.g., RCT or prediction using specific feature types [17,18]) ignores interactions between variables across views, thus, effectiveness of the prediction and intervention may vary in real-world settings. On the other hand, when various views are integrated, the dramatic difference in scale and size of views and intercorrelation between variables can hinder both feature selection and effect estimation [19–22]. To address the challenge, we propose to explore multi-view learning, an emerging machine learning technique for handling multi-view data that has different scales and representations [23–25].

Multi-view learning has been applied to integrate different medical images [26,27], multi-omics data [28–30], and multi-modal medical data (image, omics, EHR and molecular data) [31–33]. It avoids insufficient learning or overfitting due to high-dimensional and heterogenous multi-view data; and can improve model performance with complementary information among views. For example, Alkhateeb et al. [32] predicted breast cancer survival from multi-omics data by modeling each omic separately using self-organizing map and convolutional neural network (CNN) and incorporating CNN predictions with an integration layer. Multi-view learning has also been applied for feature selection to reduce data redundancy [33–36].

In this study, we developed a new multi-view learning framework for the gradient boosting method XGBoost (MV-XGB) to focus the algorithm attention on modifiable factors. It is similar to feature selection, but we mainly reduced the redundancy from non-modifiable variables and highlighted the effect of modifiable factors. Using MV-XGB, we identified important modifiable factors. Then, we developed a new strategy to analyze potential impact of modifiable factors at different times before AKI-onset, which quantifies and compares constitution of risk difference between AKI and non-AKI patients in different time windows.

2. Material and methods

2.1. Multi-view learning with XGBoost (MV-XGB)

Most multi-view learning methods are designed to improve generalization and consistency of prediction from different views; however, the objective of this study is to implement an attention-like mechanism in modeling to selectively concentrate on certain views (i.e., modifiable factors) while maintaining reliable prediction performance.

The proposed multi-view learning framework is based on XGBoost (https://github.com/dmlc/xgboost) [37], a widely-used implementation of Gradient Boosting Machine (GBM) in EHR-based prediction tasks [6,38–41]. To avoid local optimum in learning, XGBoost randomly samples a feature subset in training data in each iteration. Inspired by multi-view learning, we modified this mechanism to tune view importance by changing view weights in feature sampling during model initialization and proposed a re-weighting scheme according to importance change of features during each iteration to avoid performance degradation due to some views being excessively valued or undervalued (https://github.com/yuanborong/xgboost/tree/changed_random_seed). Algorithm details are in Supplement text S1.

2.2. Study cohort and data preprocessing

De-identified EHRs were extracted from a clinical data repository of the University of Kansas Medical Center [42,43]. Total 227,054 admissions of adults (age-at-visit $\geq$ 18) hospitalized for $\geq$ 2 days at the University of Kansas Health System (a tertiary hospital) from 2010 to 2018 were collected. AKI was defined using Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (SCr) criteria. Prediction targets were AKI onset (Yes/No) in 24 h, 48 h, 72 h respectively. Thus, for AKI patients, the data collection windows were 24 h, 48 h, 72 h before the first AKI-onset; for non-AKI patients, they were 24 h, 48 h, 72 h before the last SCr measurement. Following patients were excluded: (1) not hospitalized at the prediction point; (2) $<$ 2 SCr records during stay; (3) initial estimated Glomerular Filtration Rate (eGFR) $<$ 15 mL/min/1.73 m^2; (4) pre-existing renal failure; (5) required renal replacement therapy within 48 h of admission; (6) burn patients. Final cohorts for 24 h, 48 h, 72 h contained 144,084, 138,942, 118,036 inpatient encounters and 20,424 (14.18%), 17,350 (12.49%), 13,611 (11.53%) had AKI respectively. To test generalizability of models, 123,694, 119,200, and 101,620 encounters from year 2010–2016 were used for model training, and remaining 20,390, 19,742, 16,416 encounters from year 2017–2018 were held-out for model testing [6,39,40] (cohort characteristics in Table S1).

For each encounter, we collected data from 6 views: demographic and social history (e.g., smoking), past diagnoses, procedures, labs, medications, vitals. Procedures, labs, medications, vitals were modifiable views. We treated SCr and blood urea nitrogen (BUN) as the 7th-view because they are kidney function indicators, not modifiable factors. Procedures and past diagnoses were binary variables. Drug exposure was encoded as the most recent daily dispensing frequency before the prediction point, otherwise 0 for non-exposure. Most recent values of labs and vitals were used, and missing value was encoded as 0. Total 26,665 features were extracted, filtering those with $<$ 0.1% occurrence rate resulted in 3865–4129 features for 24 h-to-72 h datasets (Table S2). We did not perform expert knowledge-based predictor pre-selection because it will limit the algorithm ability to discover new knowledge/predictors from data. Moreover, XGBoost has been shown to be an excellent embedded feature selection method [6,40,41,44].

2.3. Analysis of modifiable factor effect in different time windows

We aimed to understand how effect of modifiable factors change with time through following steps: (1) emphasize learning on modifiable factors in prediction modeling; (2) quantify constitution of predicted risk difference between AKI and non-AKI patients in different time windows; (3) analyze how constituents of the risk difference between AKI and non-AKI patients change over time.

Correlation between modifiable and non-modifiable factors may cause underestimation of effect of modifiable factors. Thus, we enhanced the role of modifiable factors in MV-XGB by increasing the initial weights of modifiable views, and built models for 24 h, 48 h, 72 h AKI prediction (see Supplement text S2 for hyperparameter setting). To show predictive effect changes of views in MV-XGB, we analyzed proportional change of views in top-k predictors as well as change of their impact to risk prediction. We compared MV-XGB against original XGBoost (original-XGB) to ensure prediction performance did not degrade significantly after modifiable factors were valued. Area-under-the-receiver-operating-characteristic-curve (AUROC) and calibration were primary measures for the evaluation; sensitivity, specificity, precision, recall and F1 were also presented. Experiments were repeated 50 times with different random-seed.

We also compared performance of models built with top-k predictors identified by MV-XGB and original-XGB to show effectiveness of feature selection in MV-XGB. Then, we used MV-XGB to identify important modifiable features at different times. To analyze effect of a factor, sum of absolute SHAP value [45–47] (equation 3 in Supplement text S1) is

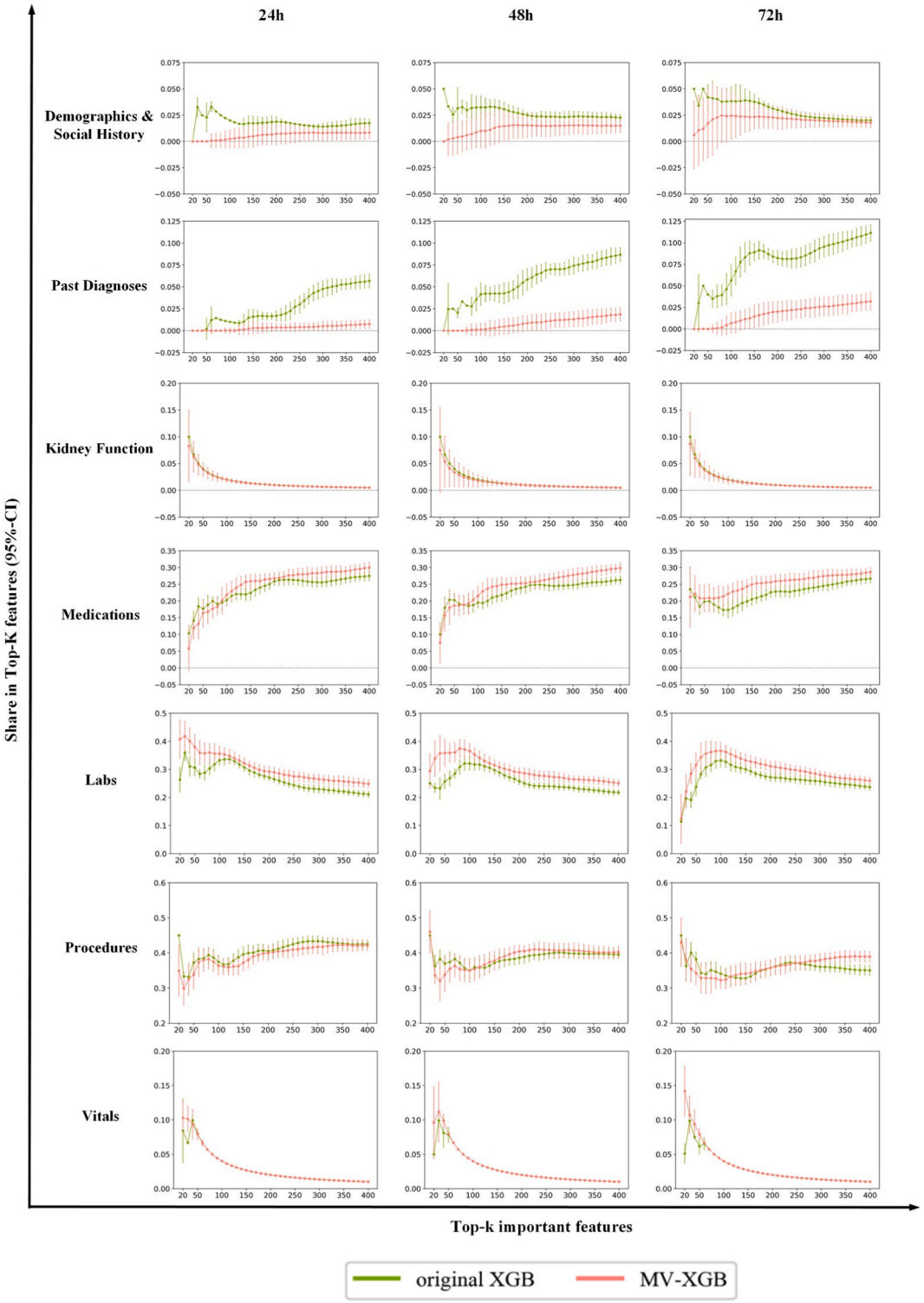

Fig. 1. Proportional change of important predictors between original and multi-view XGB.

typically used but not clinically meaningful, thus, we constructed two new indicators based on SHAP: inter-class-score-difference and exposed-score-difference (Supplement text S3). Inter-class-score-difference calculates how many predicted log-odds-ratio differences between AKI and non-AKI patients can be explained by a feature/view. It is additive, which means total predicted difference between AKI and non-AKI patients is the sum of differences from multiple views, and the difference from a single view is the sum of differences from each feature in the view. Inter-class-score-difference is sensitive to frequency of a predictor, suitable for evaluating predictor importance at the population level. In contrast, the exposed-score-difference reflects average log-odds-ratio of a predictor for an individual. Thus, we identified important modifiable features using MV-XGBs and constitution of predicted risk difference between AKI and non-AKI patients at different time points using the inter-class-score-difference and evaluated the exposure effect as well as its direction for individual using exposed-score-difference. Both indicators were calculated by averaging results from the 50 experimental repetitions.

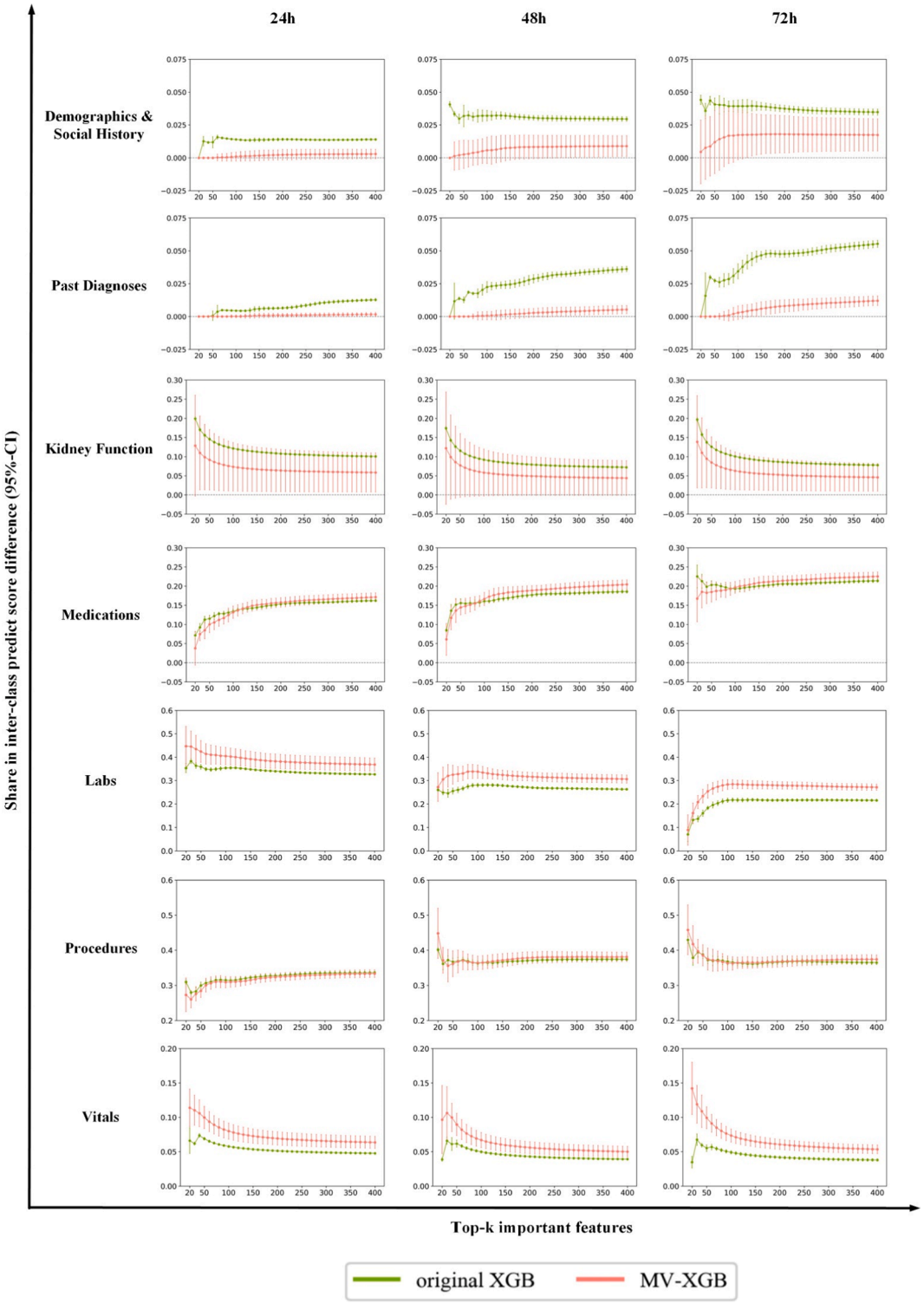

Fig. 2. Proportional change of source of inter-class prediction score difference between original and multi-view XGB.

A modifiable factor may have long/short-term effects and synergistic effect with non-modifiable factors. Since short-term effect may be more valuable for AKI prevention, we compared inter-class-score-difference of factors in 24 h, 48 h, 72 h models to understand how risk difference between AKI and non-AKI patients change across time-windows.

3. Results

3.1. Identification of modifiable factors with MV-XGB

Fig. 1& 2 demonstrate that MV- XGB can significantly enhance the role of modifiable features. Importance of non-modifiable features in demographics, social history, and past diagnoses decreased significantly in MV-XGB models, with their share in top-400 features (Fig. 1) decreased by an average of 78.4%(24 h)-61.8%(72 h) compared to

Table 1
Model performance comparison between original and multi-view XGB in predicting AKI before 24–72 h.

Prediction point	AUROC (95%-CI) of original XGB	AUROC (95%-CI) of MV-XGB	p
Before 24 h	0.859 (0.857–0.861)	0.854 (0.851–0.858)	0.02
Before 48 h	0.801 (0.799–0.803)	0.798 (0.793–0.802)	0.18
Before 72 h	0.768 (0.765–0.770)	0.765 (0.761–0.769)	0.30

original-XGB, and the decrease in effects expanded to an average of 81.5%(24 h)-67.8%(72 h) with inter-class-score-difference (Fig. 2). The impact of renal function indicators (non-modifiable) decreased by about 40% on average. As expected, contribution of the modifiable features to the inter-class-score-difference increased from 83.3% to 87.3% in original-XGB to 92.4%-94.1% in MV- XGB. Effects of labs and vitals increased more significantly, and similar results were obtained even when all modifiable views were combined.

To ensure accurate feature effect estimation, we compared MV-XGB and original-XGB in Table 1 and Fig. 3. AUROC difference between original-XGB and MV-XGB were generally insignificant, and both achieved good calibration. More comparisons are in Table S3 & S4. Models built with various top-k predictors identified by the two approaches also showed similar performance (Fig. S1), which identified ~ 200 important AKI predictors.

3.2. Temporal dynamics of modifiable risk factors

As stated earlier, inter-class-score-difference measures risk difference between AKI and non-AKI patients. Table 2 shows that inter-class-score-difference in 24 h and 72 h models were 2.879 and 1.911 respectively. That indicates risk difference between AKI and non-AKI patients at 72 h is 66.4% (1.911/2.879) of the difference at 24 h, or 38% ($e^{1.911}/e^{2.879}$) if we transform the inter-class-score-difference to predicted OR (odds-ratio) difference. Comparing results between 24 h and 48 h, the above proportions increased to 75.3% and 49.1% respectively. The effects of modifiable features at 72 h were 48.4%-86.1% when comparing their effects at 24 h (Table 2). Important modifiable features in 24 h and 72 h models were significantly different, among top-20 features (Fig. 4), shares of vitals, labs, procedures, and medications in the inter-class-score-difference changed from 11.4%, 44.7%, 27.3%, and 3.8% at 24 h to 14.2%, 8.9%, 45.8%, and 16.8% at 72 h. The effects of important modifiable features at 72 h were generally steady between 24 h and 72 h models while effects of important modifiable features at 24 h significantly decreased in 72 h model. Overall, labs and procedures contributed the most to the increase in difference

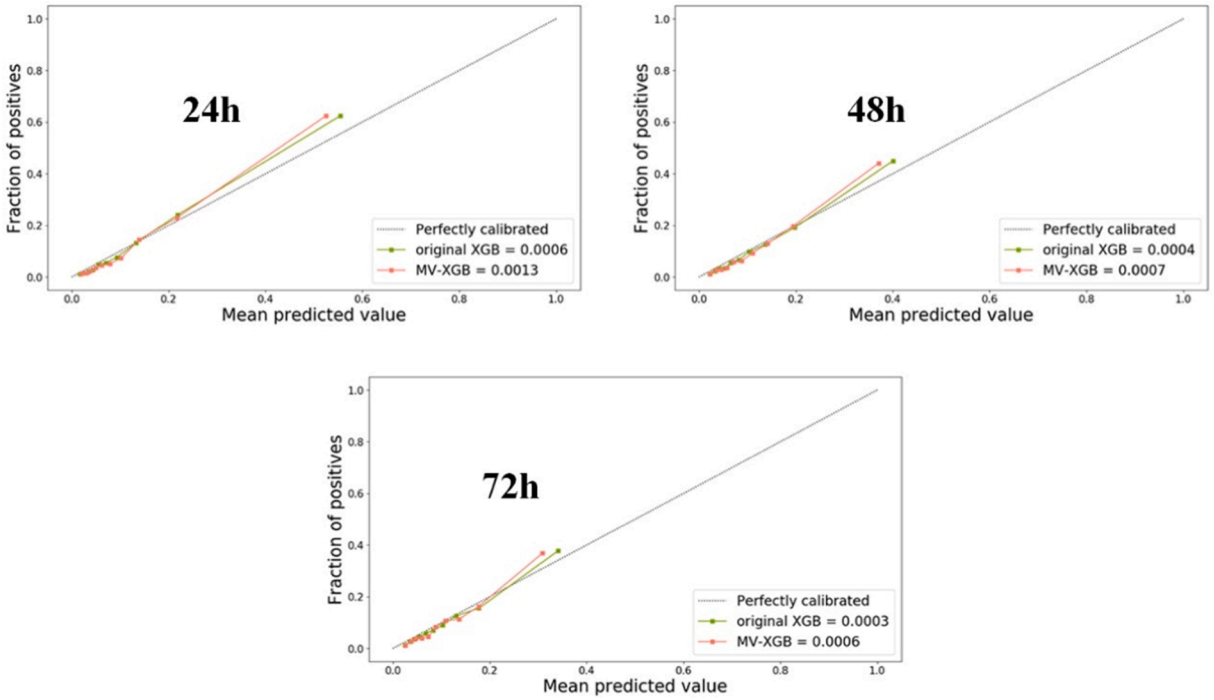

Fig. 3. Calibration comparison between original and multi-view XGB.

Table 2
Effect change of views to inter-class score difference between AKI and non-AKI patients.

Feature category	Inter-class Score Diff. in 24 h (share)	Inter-class Score Diff. in 48 h (share)	Inter-class Score Diff. in 72 h (share)	Effect in 48 h/24 h	Effect in 72 h/24 h	Account for Score Diff. decrease from 24 h to 48 h	Account for Score Diff. decrease from 24 h to 72 h
Demographics & Social History	0.009 (0.3%)	0.019 (0.9%)	0.032 (1.7%)	210.1%	348.9%	−1.4%	−2.3%
Vitals	0.174 (6.0%)	0.101 (4.7%)	0.094 (4.9%)	58.1%	54.1%	10.2%	8.2%
Kidney Function	0.161 (5.6%)	0.089 (4.1%)	0.081 (4.2%)	55.6%	50.4%	10.0%	8.2%
Labs	1.024 (35.6%)	0.638 (29.4%)	0.496 (26.0%)	62.3%	48.4%	54.4%	54.5%
Past Diagnoses	0.012 (0.4%)	0.02 (0.9%)	0.032 (1.7%)	170.7%	268.7%	−1.2%	−2.1%
Procedures	0.97 (33.7%)	0.829 (38.2%)	0.72 (37.7%)	85.5%	74.2%	19.7%	25.8%
Medications	0.53 (18.4%)	0.471 (21.7%)	0.456 (23.9%)	89.0%	86.1%	8.2%	7.6%
Total	2.879 (100.0%)	2.168 (100.0%)	1.911 (100.0%)	75.3%	66.4%	100.0%	100.0%

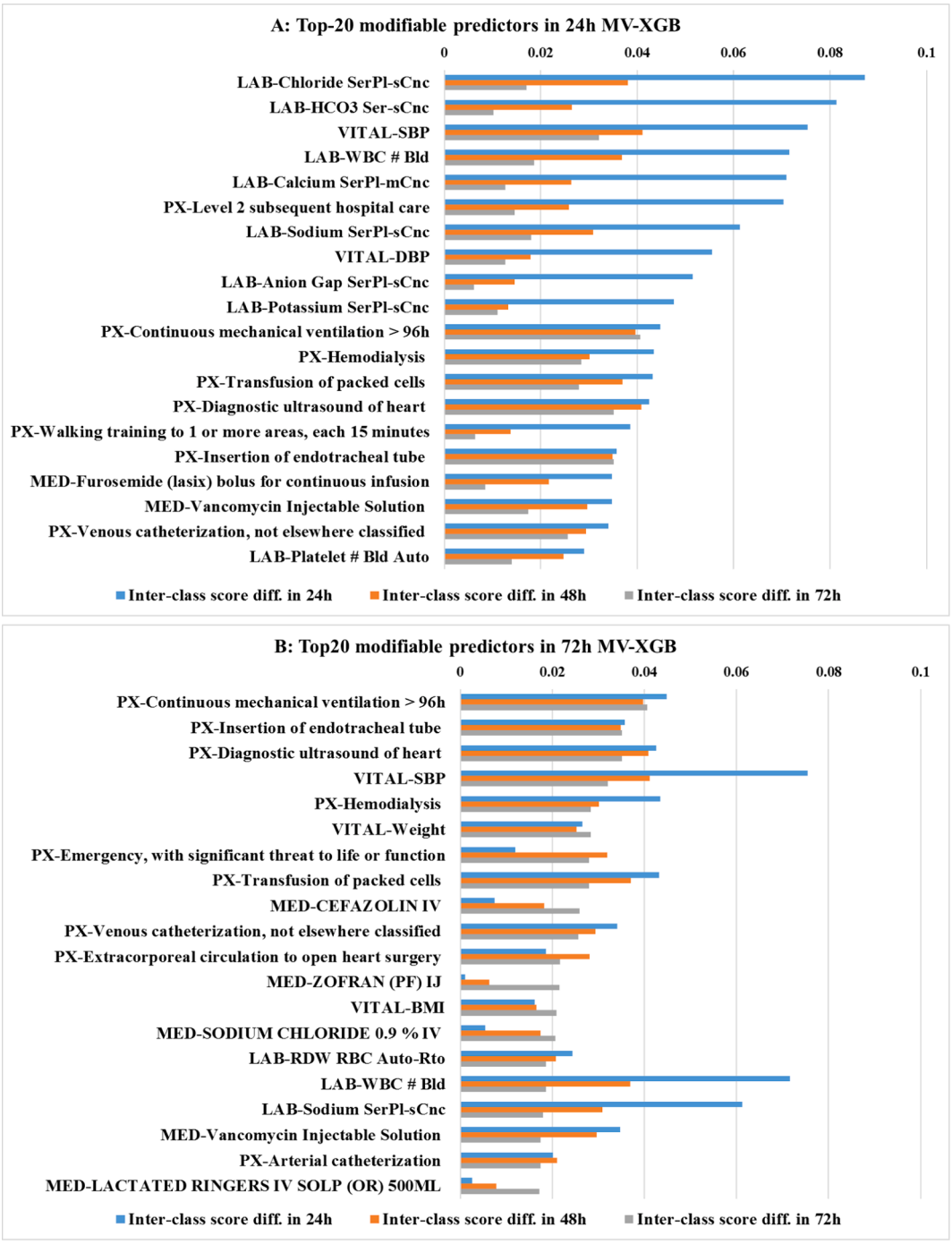

Fig. 4. Comparison of Top-20 modifiable features between MV-XGB for 24 h and 72 h.

between AKI and non-AKI patients from 72 h-to-24 h, accounting for 54.5% and 25.8% respectively with measure of inter-class-score-difference.

3.3. Important modifiable risk factors for intervention in different time windows

To determine which factors are more important to AKI prevention at different time, we investigated what increased the risk difference between AKI and non-AKI patients from 72 h-to-24 h before AKI onset. We integrated the top-50 modifiable features (highest inter-class-score-difference) at 24 h, 48 h, and 72 h, and compared their inter-class-score-difference at different time points. Based on whether inter-class-score-difference of a feature at 48 h and 72 h is over 40% of its value at 24 h, we classified them into "important modifiable features at 24–48 h" (24–48 h features, Table 3), " important modifiable features at 48–72 h" (48–72 h features, Table 3), and "features remained important longer than 72 h" (features before 72 h, Table 4). Exposed-score-difference of important medications and procedures is in Table 5 to show their effect on individuals (feature classification is the same as in Tables 3 and 4).

In Fig. 5, we combined some important modifiable features whose concepts are similar and estimated their benefits of interventions at different time windows. If we start intervening "24–48 h features" and "48–72 h features" in their respective time intervals, the inter-class-score-difference in 24 h can potentially decrease by 16.6% and 18.4% respectively. The potential decreases were primarily related to

Table 3
Important modifiable factors in 24–72 h. Factors presented in this table are union of top-50 modifiable features in MV-XGB for 24–72 h and their inter-class score difference in the 72 h model is<40% against their effect in 24 h model.

Duration of effect maintains > 40%	View	Feature	Inter-class score diff in 24 h	Inter-class score diff in 48 h	Inter-class score diff in 72 h	Effect in 48 h/24 h	Effect in 72 h/24 h
24–48 h	VITAL	DBP	0.0556	0.0179	0.0126	32.1%	22.7%
	PX	Level 2 subsequent hospital care	0.0704	0.0258	0.0146	36.6%	20.7%
		Walking training to 1 or more areas, each 15 min	0.0386	0.0137	0.0064	35.4%	16.6%
	LAB	HCO3 Ser-sCnc	0.0814	0.0265	0.0102	32.6%	12.6%
		Calcium SerPl-mCnc	0.0709	0.0264	0.0126	37.3%	17.8%
		Anion Gap SerPl-sCnc	0.0515	0.0146	0.0062	28.4%	12.0%
		Potassium SerPl-sCnc	0.0476	0.0132	0.0110	27.7%	23.0%
48–72 h	PX	Level 1 subsequent hospital care	0.0184	0.0118	0.0019	64.0%	10.5%
		Injection, piperacillin sodium/tazobactam sodium, 1 g/0. 125 g (1. 125 g)	0.0160	0.0114	0.0059	71.4%	37.1%
		High-dose infusion interleukin-2 (IL-2)	0.0120	0.0092	0.0000	76.8%	0.0%
		Collection of venous blood by venipuncture	0.0147	0.0086	0.0032	58.7%	21.5%
		X-ray of chest, frontal view	0.0142	0.0086	0.0050	60.3%	35.5%
	MED	FUROSEMIDE (LASIX) BOLUS FOR CONTINUOUS INFUSION	0.0348	0.0217	0.0085	62.3%	24.4%
		PIPERACILLIN-TAZOBACTAM-DEXTRS 4.5 GRAM/100 ML IV PGBK	0.0251	0.0134	0.0064	53.5%	25.7%
		ZOSYN 3.375 GRAM IV SOLR	0.0209	0.0126	0.0059	60.3%	28.5%
		DEXAMETHASONE SODIUM PHOS (PF) IJ	0.0138	0.0064	0.0017	46.4%	12.0%
		Aldesleukin Injection	0.0114	0.0055	0.0000	48.6%	0.0%
	LAB	Chloride SerPl-sCnc	0.0872	0.0381	0.0171	43.6%	19.6%
		WBC # Bld	0.0716	0.0369	0.0186	51.6%	26.0%
		Sodium SerPl-sCnc	0.0613	0.0309	0.0180	50.5%	29.4%

electrolyte balance [1,10] (0.330), high-risk medications [1,11,13,48–50] (0.118), care strategy (0.104, including level of subsequent hospital care and physical therapy), blood pressure [1,10–13] (0.086), infection [1,11,12] (0.067), and anemia (including transfusion of packed cells) [10,13,51] (0.046). These are all well-known AKI risk factors.

Among important modifiable factors, the changes in electrolyte balance explained most inter-class-score-difference increase (41.8% in 24–72 h, 38.3% in 24–48 h), its effect largely exists in the 24 h model, and accounted for 0.251 inter-class score-difference-change between 24 h and 48 h. Four high-risk medications were identified to be associated with higher AKI risk: *aldesleukin* (chemotherapy), *furosemide* (diuretic), *piperacillin-tazobactam* and *vancomycin* (antibiotics). *Aldesleukin, furosemide,* and *piperacillin-tazobactam* were among the "48–72 h features". *Aldesleukin* had the largest effect at the individual level (Table 5); it belonged to the "48–72 h features" because many patients had AKI soon after its exposure (Table S1). *Vancomycin* maintained a larger effect in the 72 h model against its effect in the 24 h model (50.0% according to inter-class-score-difference or 66.9% according to exposed-score-difference). This is probably due to the long elimination half-life of *vancomycin* (4–11 h), especially in patients with impaired renal function (6–10 days). Blood pressure related to hypoperfusion is known to be associated with 40% hospital-acquired AKI [1]. We found the decreasing effect of systolic pressure is slower (compared with diastolic pressure, DBP, a "24–48 h feature") and it belonged to the "features before 72 h", which may be due to its association with hypertension in older patients that have a long-term impact on the kidney. Effect of infection in 24–72 h mainly came from white blood count (WBC, explained 0.053 change of inter-class-score-difference in 24–72 h). The significant effect changes of care strategy in different time windows may indicate the variability of patient status in a short time.

From "features before 72 h", we observed features related to mechanical ventilation or respiratory failure, anemia, and cardiac procedure/condition have a strong impact on AKI (Table 5). Their effects have been studied extensively [10,13,51–56]. Our findings suggest effects of these events would last a long time. According to inter-class-score-difference, effects of features related to mechanical ventilation or respiratory failure and cardiac procedure/condition at 72 h are still>90% against their effects at 24 h, and the proportion of anemia related features is about 70% on average.

Among important medications associated with lower AKI risk in 24–72 h, only *dexamethasone* belonged to the "48–72 h features", which may help decrease the risk of inflammation for AKI [57–59]. Remaining medications belonged to "features before 72 h" (Table 4), including crystalloid solutions, antibiotics, antiemetics, drugs for constipation, anesthetics and analgesics, enoxaparin; benefits of some have been studied [1,10–13,60,61] while some are still in debate [62,63].

4. Discussion

To better support AKI prevention, we proposed a multi-view learning framework to focus learning on modifiable factors. Experiments demonstrated that our approach significantly increased effect of modifiable factors while maintaining a high prediction performance. Our modifiable factor discovery approach is applicable to any EHR dataset that has modifiable characteristics and time-series record. MV-XGB can take input data one normally uses for XGBoost or any traditional machine learning algorithm, but users need to assign feature indexes to different views.

To better estimate effect of modifiable factors, we comprehensively considered EHR features for modeling. We found at least top-200 features is valuable for AKI prediction. The number of predictors reflected the complex mechanism and high prevalence of AKI in various patients. Some important modifiable factors whose concepts are similar can be combined to reduce the number of factors for analysis. Also, there may be less predictors when analyzing more homogeneous subpopulations where there is a shared AKI cause.

We analyzed important modifiable factors that can be used for improving AKI prevention in current clinical practice and how their effects change over time. Results showed that in the 24–72 h window, electrolyte balance, renal hypoperfusion, infection, high-risk medications and anemia are more important to intervene for AKI prevention. It is well-known that electrolyte balance is critical for adequate functioning of nerve and organs and its change is associated with kidney dysfunction. Most guidelines for AKI prevention consider electrolyte balance as an important factor in fluid management [1,10–13]. However, current target for fluid management is to avoid renal hypoperfusion; while our results showed that the potential gap for improving

Table 4
Important modifiable factors that maintained 40% inter-class score difference after 72 h.

View	Feature	Inter-class score diff in 24 h	Inter-class score diff in 48 h	Inter-class score diff in 72 h	Effect in 48 h/ 24 h	Effect in 72 h/ 24 h
VITAL	SBP	0.0754	0.0411	0.0321	54.5%	42.5%
	Weight	0.0265	0.0253	0.0283	95.5%	106.9%
	BMI	0.0162	0.0166	0.0209	102.8%	129.2%
PX	Continuous mechanical ventilation > 96 h	0.0448	0.0397	0.0406	88.6%	90.7%
	Insertion of endotracheal tube	0.0358	0.0349	0.0351	97.3%	98.1%
	Diagnostic ultrasound of heart	0.0425	0.0409	0.0351	96.1%	82.6%
	Hemodialysis	0.0435	0.0301	0.0284	69.1%	65.2%
	Emergency, with significant threat to life or function	0.0120	0.0319	0.0280	266.1%	234.0%
	Transfusion of packed cells	0.0432	0.0370	0.0279	85.6%	64.5%
	Venous catheterization, not elsewhere classified	0.0341	0.0294	0.0256	86.3%	75.1%
	Extracorporeal circulation to open heart surgery	0.0186	0.0281	0.0217	151.3%	116.8%
	Arterial catheterization	0.0202	0.0210	0.0174	104.3%	86.2%
	Single internal mammary-coronary artery bypass	0.0114	0.0130	0.0148	113.6%	129.4%
	Injection, ondansetron hydrochloride, per 1 mg	0.0009	0.0050	0.0142	576.7%	1647.5%
	Respiratory Ventilation > Consecutive 96 h	0.0128	0.0141	0.0140	110.6%	109.4%
	Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening	0.0106	0.0104	0.0105	98.8%	99.4%
	Percutaneous abdominal drainage	0.0087	0.0101	0.0104	116.3%	120.3%
	Insertion of Infusion Device into Superior Vena Cava, Percutaneous Approach	0.0109	0.0118	0.0099	107.5%	90.1%
MED	CEFAZOLIN IV	0.0075	0.0182	0.0259	241.0%	342.8%
	ZOFRAN (PF) IJ	0.0011	0.0063	0.0215	557.2%	1907.4%
	SODIUM CHLORIDE 0.9 % IV	0.0054	0.0175	0.0206	322.0%	379.7%
	Vancomycin Injectable Solution	0.0348	0.0296	0.0174	85.2%	50.0%
	LACTATED RINGERS IV SOLP (OR) 500ML	0.0026	0.0078	0.0172	295.8%	653.1%
	MILK OF MAGNESIA CONCENTRATED PO	0.0152	0.0181	0.0170	119.2%	111.7%
	ENOXAPARIN 40 MG/0.4 ML SC SYRG	0.0038	0.0143	0.0155	375.0%	407.4%
	BISA-LAX RE	0.0052	0.0041	0.0120	78.6%	230.3%
	FENTANYL CITRATE (PF) 2500 MCG/50 ML PCA	0.0036	0.0035	0.0113	96.1%	310.6%
	SENNALAX-S 8.6–50 MG PO TAB	0.0108	0.0115	0.0095	106.6%	87.9%
	MARDOL 325 MG PO TAB	0.0075	0.0118	0.0095	156.6%	126.1%
	OXYCODONE 5 MG PO TBOR	0.0114	0.0051	0.0077	44.6%	68.1%
	PROPOFOL 10 MG/ML IV EMUL 50 ML (INFUSION)(AM) (OR)	0.0114	0.0075	0.0071	65.3%	62.5%
	FUROSEMIDE 200 MG IN D5W 100 ML IV DRIP	0.0131	0.0095	0.0055	72.8%	42.2%
LAB	RDW RBC Auto-Rto	0.0244	0.0208	0.0186	85.1%	76.4%
	Bilirub SerPl-mCnc	0.0290	0.0161	0.0150	55.6%	51.6%
	Platelet # Bld Auto	0.0290	0.0248	0.0140	85.4%	48.4%
	Hct VFr Bld Auto	0.0179	0.0154	0.0140	85.7%	78.2%
	Hgb Bld-mCnc	0.0144	0.0137	0.0132	95.1%	91.4%
	BNP Bld-mCnc	0.0241	0.0166	0.0131	68.9%	54.4%
	RBC # Bld Auto	0.0162	0.0146	0.0113	89.8%	69.7%
	Lymphocytes/leuk NFr Bld Auto	0.0178	0.0133	0.0109	74.5%	61.4%
	aPTT PPP	0.0092	0.0101	0.0101	109.6%	109.4%
	Albumin SerPl BCG-mCnc	0.0095	0.0118	0.0096	124.3%	100.6%
	ALP SerPl-cCnc	0.0101	0.0089	0.0092	88.1%	90.6%
	Lymphocytes # Bld Auto	0.0157	0.0121	0.0091	77.4%	57.8%
	Neutrophils # Bld Auto	0.0097	0.0079	0.0087	82.2%	90.4%
	Magnesium SerPl-mCnc	0.0127	0.0115	0.0073	90.8%	57.6%
	AST SerPl-cCnc	0.0130	0.0071	0.0069	54.5%	53.4%

AKI prevention is larger in electrolyte balance than in renal hypoperfusion. KDIGO Guideline also discussed the role of electrolyte balance in timing of renal replacement therapy [1]. Our findings reiterate the importance of continuous monitoring the electrolyte status of high-risk patients and addressing the abnormalities in a timely fashion.

Blood pressure is related to renal perfusion, and in current recommendations, their targets are measured by mean arterial pressure or systolic pressure [11,12]. However, baseline systolic pressure may be influenced by the higher correlation between systolic pressure and hypertension in older patients. Our results suggest that we can consider a potentially more sensitive target based on diastolic pressure.

Antibiotics treats infection but can be nephrotoxic, thus, it is important to balance the benefit and risk of its use. We found exposure to *vancomycin* and *piperacillin-tazobactam* generally related to higher AKI risk. *Vancomycin* is a well-known nephrotoxin and the nephrotoxicity increases when it is jointly used with other antibiotics like *tazobactam* [48,49]. *Vancomycin* has a much longer elimination half-life than other common antibiotics, especially in patients with impaired renal function. Our results showed that *vancomycin* can maintain a large effect in 72 h model against its effect in 24 h model. It indicates *vancomycin* should be used carefully in patients at high AKI risk to prevent long-term nephrotoxicity and unexpected medication interaction.

In this study, most medications potentially important for renal protection belonged to "features last>72 h" (except *dexamethasone*). Benefits of medications like crystalloid solutions, antibiotics, anesthetics and analgesics, enoxaparin have been studied while some is still in debate. However, many of the drugs identified had a much larger effect at 72 h against their effect at 24 h. Further research for these drugs may need to consider the time windows of their usages for AKI prevention.

Risks of blood transfusion, mechanical ventilation, and cardiac surgery can last several days, but they are also life-saving procedures, thus it is more important to control their risk factors (e.g., blood loss and pneumonia). For patients requiring these procedures, we should evaluate and monitor their risk factors in a longer time frame.

5. Limitation

First, the study is based on retrospective observational EHR data,

Table 5
Exposed score difference of important medication and procedure in the union of top-50 modifiable features.

Duration of effect (same as Table 4)	View	Feature	Exposed score diff. in 24 h	Exposed score diff. in 48 h	Exposed score diff. in 72 h	Effect in 48 h/ 24 h	Effect in 72 h/ 24 h
24–48 h	PX	Level 2 subsequent hospital care	−0.2985	−0.1700	−0.1186	56.9%	39.7%
		Walking training to 1 or more areas, each 15 min	−0.3436	−0.2011	−0.1214	58.5%	35.3%
48–72 h	PX	Level 1 subsequent hospital care	−0.1752	−0.1406	−0.0376	80.3%	21.5%
		Injection, piperacillin sodium/tazobactam sodium, 1 g/0. 125 g (1. 125 g)	0.1661	0.1448	0.0884	87.2%	53.2%
		High-dose infusion interleukin-2 (IL-2)	0.8971	1.0316	0.0000	115.0%	0.0%
		Collection of venous blood by venipuncture	−0.0873	−0.0603	−0.0249	69.1%	28.6%
		X-ray of chest, frontal view	0.0504	0.0384	0.0170	76.2%	33.8%
	MED	FUROSEMIDE (LASIX) BOLUS FOR CONTINUOUS INFUSION	0.1770	0.1317	0.0686	74.4%	38.8%
		PIPERACILLIN-TAZOBACTAM-DEXTRS 4.5 GRAM/100 ML IV PGBK	0.2211	0.1479	0.0832	66.9%	37.6%
		ZOSYN 3.375 GRAM IV SOLR	0.2074	0.1579	0.0891	76.1%	43.0%
		DEXAMETHASONE SODIUM PHOS (PF) IJ	−0.1434	−0.0773	−0.0228	53.9%	15.9%
		Aldesleukin Injection	0.7694	0.6283	0.0000	81.7%	0.0%
>72 h	PX	Continuous mechanical ventilation > 96 h	0.6208	0.6143	0.6038	99.0%	97.3%
		Insertion of endotracheal tube	0.3140	0.3360	0.3440	107.0%	109.6%
		Diagnostic ultrasound of heart	0.2452	0.2556	0.2363	104.2%	96.4%
		Hemodialysis	1.5653	1.5640	1.5998	99.9%	102.2%
		Emergency department visit, with significant threat to life or function	−0.0912	−0.1719	−0.1543	188.5%	169.2%
		Transfusion of packed cells	0.3495	0.3338	0.2812	95.5%	80.5%
		Venous catheterization, not elsewhere classified	0.3280	0.3274	0.2965	99.8%	90.4%
		Extracorporeal circulation auxiliary to open heart surgery	0.3141	0.3824	0.3990	121.8%	127.0%
		Arterial catheterization	0.2172	0.2517	0.2220	115.9%	102.2%
		Single internal mammary-coronary artery bypass	0.3046	0.3140	0.4201	103.1%	137.9%
		Injection, ondansetron hydrochloride, per 1 mg	0.0286	−0.0319	−0.0768	−111.5%	−268.2%
		Respiratory Ventilation > Consecutive 96 h	0.7064	0.8651	0.8691	122.5%	123.0%
		Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening	0.4318	0.4978	0.5181	115.3%	120.0%
		Percutaneous abdominal drainage	0.1946	0.2518	0.2576	129.4%	132.4%
		Insertion of Infusion Device into Superior Vena Cava, Percutaneous Approach	0.4382	0.5031	0.4426	114.8%	101.0%
	MED	CEFAZOLIN IV	−0.0502	−0.1239	−0.1619	246.8%	322.5%
		ZOFRAN (PF) IJ	0.0102	−0.0295	−0.0881	−288.5%	−861.5%
		SODIUM CHLORIDE 0.9 % IV	−0.0787	−0.0978	−0.0995	124.2%	126.5%
		Vancomycin Injectable Solution	0.2007	0.1920	0.1342	95.7%	66.9%
		LACTATED RINGERS IV SOLP (OR) 500ML	−0.0089	−0.0452	−0.0851	508.5%	958.8%
		MILK OF MAGNESIA CONCENTRATED PO	−0.0810	−0.1044	−0.0979	128.9%	120.9%
		ENOXAPARIN 40 MG/0.4 ML SC SYRG	−0.0256	−0.0840	−0.0851	327.5%	331.9%
		BISA-LAX RE	−0.0323	−0.0259	−0.0688	80.2%	213.1%
		FENTANYL CITRATE (PF) 2500 MCG/50 ML PCA	−0.0156	−0.0121	−0.0468	77.3%	299.3%
		SENNALAX-S 8.6–50 MG PO TAB	−0.0759	−0.0757	−0.0708	99.7%	93.3%
		MARDOL 325 MG PO TAB	−0.0356	−0.0573	−0.0445	161.0%	124.9%
		OXYCODONE 5 MG PO TBOR	−0.0612	−0.0311	−0.0457	50.9%	74.6%
		PROPOFOL 10 MG/ML IV EMUL 50 ML (INFUSION)(AM)(OR)	−0.0824	−0.0561	−0.0466	68.1%	56.5%
		FUROSEMIDE 200 MG IN D5W 100 ML IV DRIP	0.4741	0.4470	0.3156	94.3%	66.6%

results should only be interpreted for identifying potential gap in current clinical practice at a single center; difference in patient population and management in other hospitals may influence the result [6]. Difference of importance modifiable factors in different centers and subpopulation is an interesting topic for further research. Our result does not reflect importance of modifiable factors for an individual. To understand this question, we need to combine our proposed method and personalized modeling. Second, only three prediction points were considered. Third, we did not consider intercorrelation among modifiable factors, which may influence their effect estimation. Fourth, to accurately estimate effect of modifiable factors, we comprehensively considered EHR features for modeling, but we primarily analyzed the result of important features, less important features that are similar in concept to important ones may be ignored; further study can use ontology to integrate feature with similar concepts.

6. Summary table

What was already known on the topic

Many risk factors of hospital-acquired AKI are known.
Some clinical guidelines for AKI management have been proposed.
Effectiveness of AKI prediction with electronic health records have been verified.

What this study added to our knowledge

A multi-view analysis approach for better identification of modifiable risk factors.
Identified gap in improvement for current AKI prevention strategy.
Analyzed what modifiable factors are more important at various time points prior to AKI onset.

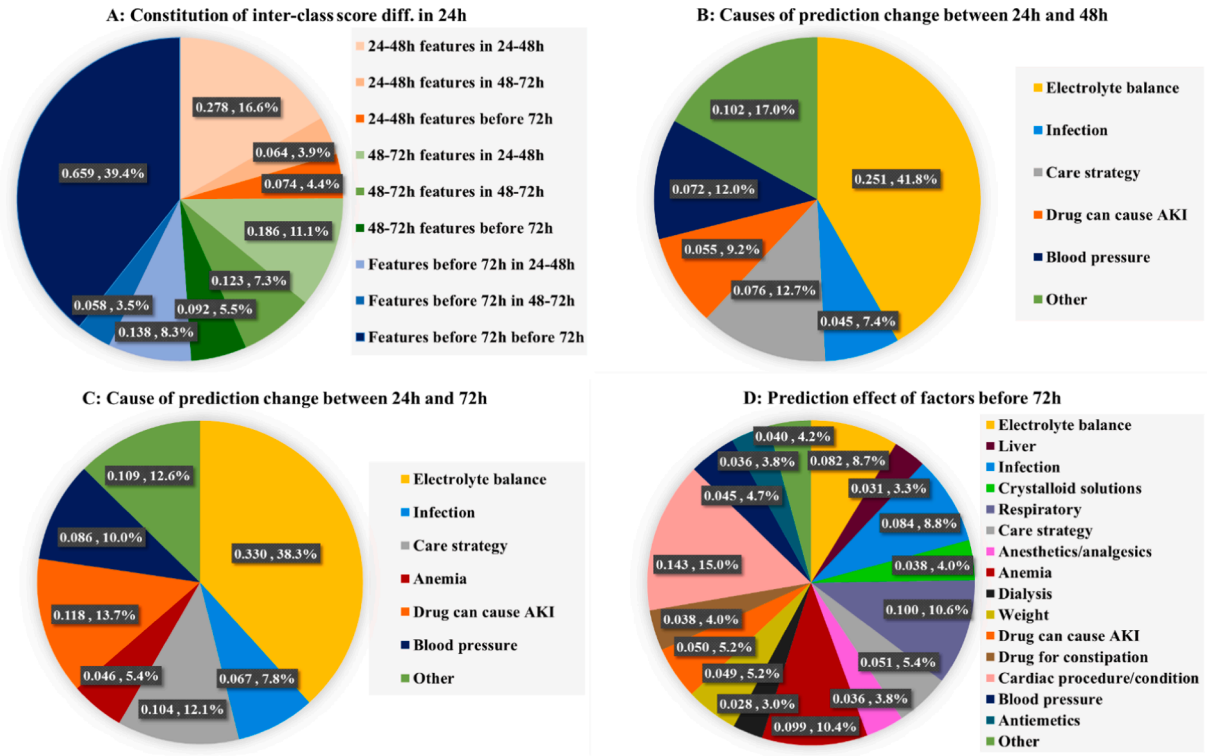

Fig. 5. Factors related to inter-class score difference increase in different time windows. Results in this figure were based on union of top-50 modifiable features in MV-XGB for 24–72 h. Inter-class score difference of factors and its share (%) in all important predictors is presented. The percentages were calculated by dividing change of inter-class score different in a specific class of important factors by change of inter-class score different in all important predictors. In (A)-(C), only effect change of predictors increased inter-class score difference from 72 h to 24 h were considered.

7. Data availability

The de-identified clinical dataset used in this study is not publicly available and restrictions apply to its use. The de-identified dataset may be made available for research, subjective to data governance and ethical approvals from the University of Kansas Medical Center.

8. Code availability

Programming codes for important experiments in this study are available in https://github.com/yuanborong/xgboost/tree/changed_random_seed.

9. Authors' contributions

ML and YH initiated the project and designed the overall study. ML, XZ, WC, BY performed the data acquisition and processing. KL, BY, LP, XZ performed algorithm implementation, modeling, and analysis. KL, BY drafted the manuscript, with critical revision advices on important intellectual content from YH and ML. ML confirm to have full access to the raw de-identified dataset from the University of Kansas Medical Center. KL, BY confirm that they had access to intermediate processed dataset for model development and analysis. All authors gave final approval of the version to be submitted.

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