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A web-based machine-learning algorithm predicting postoperative acute kidney injury after total knee arthroplasty

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Abstract

Purpose Acute kidney injury (AKI) is a deleterious complication after total knee arthroplasty (TKA). The purposes of this study were to identify preoperative risk factors and develop a web-based prediction model for postoperative AKI, and assess how AKI affected the progression to ESRD.

Method The study included 5757 patients treated in three tertiary teaching hospitals. The model was developed using data on 5302 patients from two hospitals and externally validated in 455 patients from the third hospital. Eighteen preoperative variables were collected and feature selection was performed. A gradient boosting machine (GBM) was used to predict AKI. A tenfold-stratified area under the curve (AUC) served as the metric for internal validation. Calibration was performed via isotonic regression and evaluated using a calibration plot. End-stage renal disease (ESRD) was followed up for an average of 41.7 months.

Results AKI develops in up to 10% of patients undergoing TKA, increasing the risk of progression to ESRD. The ESRD odds ratio of AKI patients (compared to non-AKI patients) was 9.8 (95% confidence interval 4.3–22.4). Six key predictors of postoperative AKI were selected: higher preoperative levels of creatinine in serum, the use of general anesthesia, male sex, a higher ASA class (> 3), use of a renin–angiotensin–aldosterone system inhibitor, and no use of tranexamic acid (all $p < 0.001$). The predictive performance of our model was good (area under the curve 0.78 [95% CI 0.74–0.81] in the developmental cohort and improved in the external validation cohort (0.89). Our model can be accessed at https://safetka.net.

Conclusions A web-based predictive model for AKI after TKA was developed using a machine-learning algorithm featuring six preoperative variables. The model is simple and has been validated to improve both short- and long-term prognoses of TKA patients. Postoperative AKI may lead to ESRD, which surgeons should strive to avoid.

Level of evidence Diagnostic level II.

Keywords Acute kidney injury · Total knee arthroplasty · Total knee replacement · Machine learning · Prediction · End-stage renal disease

Introduction

The reported complications of total knee arthroplasty (TKA) include deep vein thrombosis, a need for transfusion, infection, and acute kidney injury (AKI), but most are rare [2]. Of these complications, AKI is an independent risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD), both of which are life-threatening and increase the duration of hospitalization [4, 5]. The risk-adjusted 90-day mortality was higher for patients with than without AKI (6.5 vs. 4.4%) [9]. The incidence of AKI after TKA is 5–10% [7, 23, 27]. The measures taken to prevent or delay AKI include maintenance of appropriate blood pressure and volume,

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correction of anemia, and good oxygenation of tissue [15, 16]. Despite such efforts, however, AKI requires active management in high-risk groups.

Electronic medical records (EMRs) accumulate massive amounts of data, facilitating machine-learning and the use of artificial intelligence [8, 12, 25]. Machine-learning models for prediction of AKI have also been developed; these have performed better than logistic regression for hospitalized patients and patients undergoing major surgery [14, 18, 21, 24]. However, these models do not target TKA patients, have not performed well, and have employed impractical variables. In addition, all of these models were based on data from single centers and thus lack external validation. Moreover, the models use data that can be collected only retrospectively such as operating times [21] and length of hospital stay [17]. It remains unclear whether machine-learning models can reliably improve patient prognoses in daily clinical practice.

This study examined the hypotheses that (1) there is a high-risk group of AKI after TKA and AKI is associated with the subsequent development of ESRD, and (2) postoperative AKI can be predicted through machine-learning using only preoperative information. The purposes of this study were (1) to identify key preoperative risk factors for AKI development, (2) to develop and validate a machine-learning model predicting postoperative AKI in TKA patients, (3) to assess how AKI affected the progression to ESRD, and 4) to provide an easy-to-use web-based program for orthopedic surgeons.

Materials and methods

Study population

The study population included patients who underwent TKA at three teaching hospitals. The developmental cohort included patients from two institutions treated from January 2012 to May 2019, and the validation cohort included patients from a third institution treated from June 2018 to May 2019. Patients who had undergone either unilateral or bilateral TKA were enrolled. Patients with established ESRD, for whom data regarding serum levels of creatinine were lacking, with stage 5 chronic kidney disease, and with preoperative serum levels of creatinine exceeding 4 mg/dL were excluded. Patients with ESRD were identified using the Korean Society of Nephrology registry [11].

A total of 5924 patients were screened for inclusion (2527, 2942, and 455 from institutions 1–3, respectively). After the exclusion criteria had been applied, 5302 patients from institutions 1 and 2 were assigned to the developmental cohort and the 455 patients from the institution 3 were assigned to the validation cohort (Fig. 1). The baseline characteristics of both cohorts are listed in Table 1. The mean

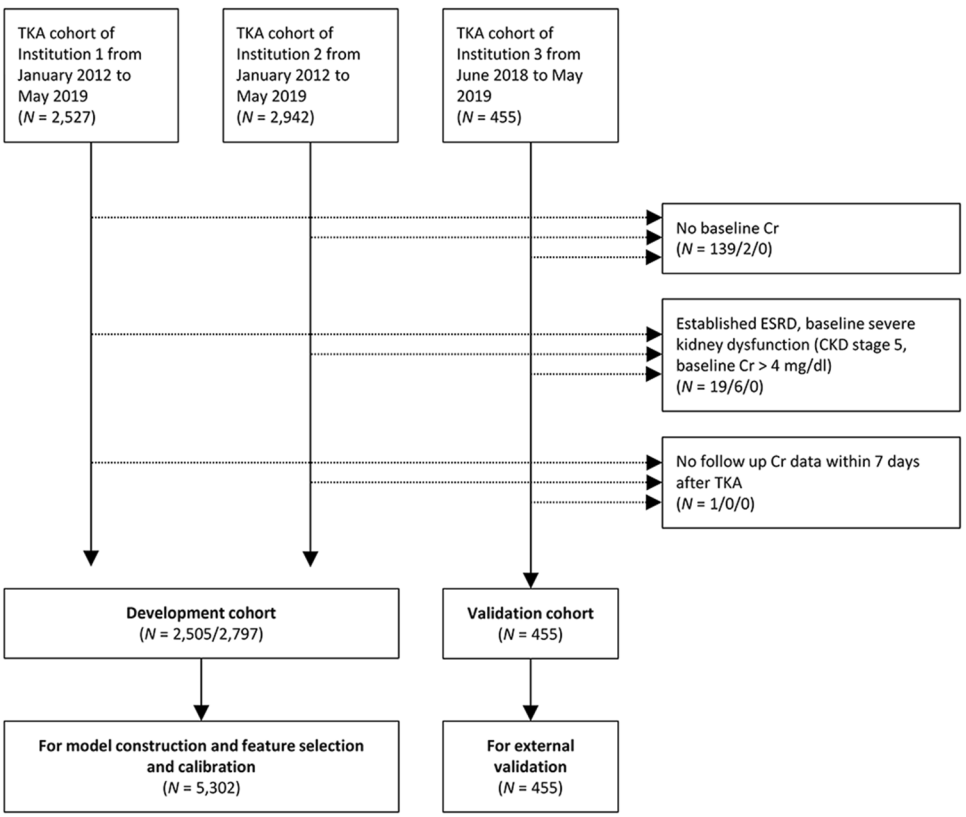

Fig. 1 The study population. *TKA* total knee arthroplasty, *Cr* creatinine, *ESRD* end-stage renal disease *CKD* chronic kidney disease

Table 1 Baseline characteristics of the developmental and validation cohorts

Characteristics	Developmental cohort ($N=5302$)		Validation cohort ($N=455$)		p-value
	Value	Missing	Value	Missing	
Age (SD)	71.1 (6.9)	–	71.3 (6.0)	–	n.s
Sex					
M	610 (12%)	–	72 (16%)	–	0.006
F	4692 (88%)		383 (84%)		
BMI (SD)	26.8 (3.5)	–	27.1 (3.7)	12	n.s
Type of surgery					
Unilateral	2867 (54%)	–	308 (68%)	–	< 0.001
Staged bilateral	2142 (40%)		144 (32%)		
Contemporaneous bilateral	293 (6%)		3 (1%)		
ASA class					
1	756 (15%)	146 (3%)	54 (12%)	5 (1%)	n.s
2	4072 (79%)		361 (80%)		
3	325 (6%)		35 (8%)		
4	3 (0%)		0 (0%)		
Type of anesthesia					
General	232 (4%)	3 (0%)	25 (5%)	–	n.s
Spinal	5067 (96%)		430 (95%)		
Diabetes mellitus					
Y	1162 (22%)	–	116 (28%)	47 (10%)	0.002
N	4140 (78%)		292 (72%)		
Use of NSAIDs					
Y	2310 (44%)	–	166 (36%)	–	0.003
N	2992 (56%)		289 (64%)		
Use of antithrombotics					
Y	1350 (25%)	-	103 (23%)	–	n.s
N	3952 (75%)		352 (77%)		
Use of RAASis					
Y	1878 (35%)	–	195 (43%)	–	0.002
N	3424 (65%)		260 (57%)		
Use of diuretics					
Y	540 (10%)	–	75 (16%)	–	< 0.001
N	4762 (90%)		380 (84%)		
Use of tranexamic acid					
Y	3309 (62%)	–	372 (82%)	–	< 0.001
N	1993 (38%)		83 (18%)		
Use of a statin					
Y	1706 (32%)		301 (66%)		0.030
N	3596 (68%)		154 (34%)		
BUN (SD)	17.6 (5.7)	1 (0)	17.0 (5.6)	4 (1)	0.048
Creatinine (SD)	0.8 (0.2)	–	0.8 (0.3)	–	n.s
eGFR (SD)	80.8 (16.3)	–	82.0 (16.0)	–	n.s
Hemoglobin (SD)	12.9 (1.3)	1 (0)	12.9 (1.3)	5 (1)	n.s
Platelets (SD)	244.5 (61.7)	5 (0)	248.3 (63.4)	5 (1)	n.s

**AKI* acute kidney injury, *SD* standard deviation, *BMI* body mass index, *ASA class* American Society of Anesthesiologists classification, *NSAIDs* non-steroidal anti-inflammatory drugs, *RAASis* renin–angiotensin–aldosterone system inhibitors, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate

ages were 71.1 [standard deviation (SD) 6.9] years in the development cohort and 71.3 (SD 6.0) in the validation cohort. Men comprised 12% and 16% of the development and validation cohorts, respectively; the corresponding BMI values were 26.8 (SD 3.5) and 27.1 (SD 3.7) kg/m^2.

To compare the prognoses between the AKI and non-AKI groups, patients who progressed to ESRD through March 2020 were followed. Patients with ESRD were identified using the Korean Society of Nephrology registry [11].

Surgical protocol

Antiplatelet agents including aspirin, warfarin, clopidogrel, heparin and Factor Xa inhibitors were discontinued 7 days before surgery. The developmental cohort was treated via either a parapatellar or mid-vastus approach depending on the surgeons' preferences. A posteriorly stabilized implant was placed in more than 90% of cases and cruciate retaining implant was used in remaining cases. The validation cohort was treated via a parapatellar approach and a posteriorly stabilized implant was placed in all cases. One gram of intra-articular tranexamic acid (TXA) was given unless contraindicated by TXA allergy; a history of deep vein thrombosis, pulmonary embolism, or ischemic cardiac or cerebrovascular disease; and/or a glomerular filtration rate (GFR) less than 60 mL/min. Continuous passive motion (CPM) was applied 1 day after surgery. Ambulation was permitted 12 h after surgery. TXA was administered intravenously (10 mg/kg). CPM commenced 2 days after surgery when the drain was removed.

Outcomes

The primary outcomes were development of AKI of any grade (stages 1–3) during the first postoperative week, and the effects of AKI on progression to ESRD. AKI was defined using the creatinine criteria for serum of the Kidney Disease-Improving Global Outcomes (KDIGO) group [13]. The baseline value was the last preoperative level within 6 months before surgery. KDIGO urine output criteria were not applied. The effect of AKI on the development of ESRD was assessed using the odds ratio.

Predictor variables

Eighteen preoperative variables were initially chosen as candidate predictors based on the findings in previous studies [1, 10]. The demographic data included age, sex, and body mass index (BMI). The type of surgery, American Society of Anesthesiologists Classification (ASA Class), type of anesthesia (general or spinal), and diabetes mellitus status were extracted from preoperative records. The types of surgery included unilateral, staged bilateral (1-week interval), and simultaneous bilateral TKA. Blood urea nitrogen (BUN), creatinine, hemoglobin, and platelet levels were extracted from laboratory results (the latest values within 6 months before surgery). The GFR was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [19]. To explore preoperative medication status, admission records were combined with in-hospital drug prescriptions. The drugs were classified into six categories: nonsteroidal anti-inflammatory drugs (NSAIDs), renin–angiotensin–aldosterone system inhibitors (RAASis), diuretics, antithrombotic agents, TXA, and statins. NSAIDs, RAASis, and diuretics are nephrotoxic agents; antithrombotic agents and TXA affect intraoperative bleeding. Statins were examined separately, because many reports have indicated that these protect against AKI [3, 22]. Drug categorization was based on the Anatomical Therapeutic Chemical (ATC) classification. For RAASis, angiotensin-converting-enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) were combined. The drug details are listed in Supplemental Table 1.

Statistical analyses

All statistical analyses were performed using IBM SPSS statistics ver. 25 (IBM Corp., USA). A gradient boosting machine (GBM) was used to predict the probability of AKI, employing all predictor variables. GBM uses a series of decision trees, where each tree corrects the residuals of the previous trees. After each boost, the weights are recalculated. Python 3.7 was used to encode the machine-learning algorithm. Missing values were imputed using a built-in GBM algorithm. Three feature-selection methods were used: recursive feature elimination, forward elimination, and backward elimination. The stratified K-fold ($K = 10$) approach was used to measure predictive performance; the area under the curve (AUC) of the receiver operating characteristic (ROC) curve served as the metric. The Youden index was used to identify the optimal ROC curve threshold [26]. External validation was performed using all data from one institution as a test set ($n = 455$). Calibration was performed using the isotonic regression method and evaluated by drawing a calibration plot.

Our model on the web

Figure 2 shows a schematic of our website. The Eli-5 library was used to weigh each feature.

Results

Table 2 shows the baseline characteristics of the two cohorts. Of the 5,302 patients, 539 (10.2%) were diagnosed with AKI after TKA. The AKI stages are listed in Table 3.

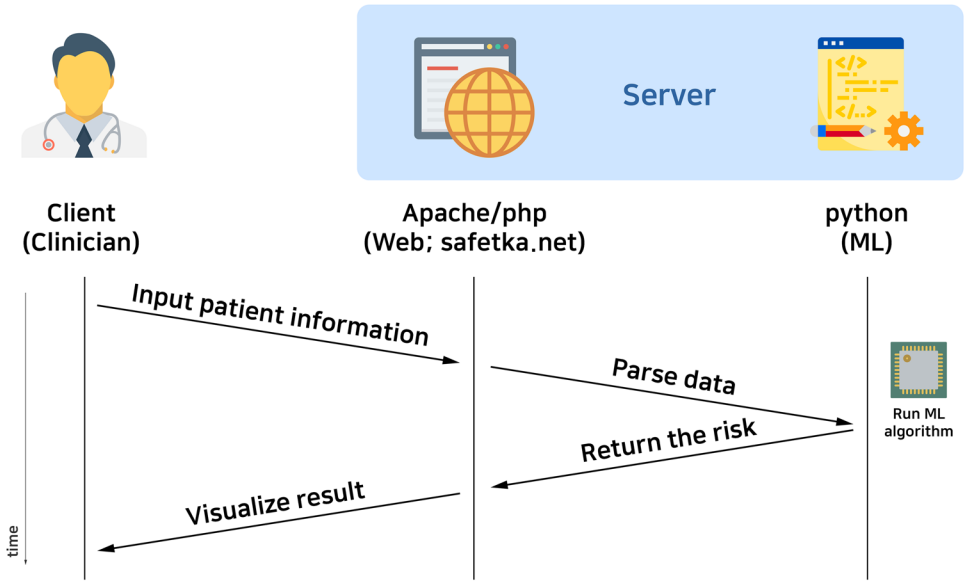

Fig. 2 Schematic diagram of our Web service. When a clinician inputs patient information, the server parses the data to Python. The risk for acute kidney injury is calculated, returned, and made visible

The registry database indicated that 12 AKI (2.2%) and 11 non-AKI (0.2%) patients progressed to ESRD (average 41.7 ± 18.5 months). The ESRD odds ratio for the AKI group, compared to the non-AKI group, was 9.8 (95% confidence interval [CI] 4.3–22.4).

Of the 18 variables, six key predictors were selected for the model: preoperative serum creatinine levels, use of TXA, general anesthesia, use of RAASis, ASA class, and sex. The GBM importance plot is shown in Fig. 3. The stratified tenfold AUC was 0.78 (0.74–0.81) after internal validation of the developmental cohort. The final model exhibited an optimal threshold of 0.098. The sensitivity and specificity of internal validation were 0.65 and 0.77, respectively. When AKI was predicted in the validation cohort, the AUC was 0.89. The sensitivity and specificity of external validation at the same threshold were 0.92 and 0.78. Calibration plot is shown in Supplemental Fig. 1. Our model may be found at https://safetka.net. When a user enters the six key variables, the model returns the probability of postoperative AKI, whether the patient is at high risk for postoperative AKI, and the weights of each of the six variables (Fig. 4).

Discussion

The most important finding of this study was that postoperative AKI may lead to ESRD, and that this risk can be predicted preoperatively by a machine-learning algorithm. This algorithm can also be applied in independent institutions, because the predictive performance was maintained in external validation. Thus, this algorithm can be used to improve both the short- and long-term prognoses of TKA patients.

Six key preoperative variables to predict AKI after TKA were incorporated into a machine-learning algorithm; for the developmental cohort, the model yielded a stratified tenfold AUC of 0.78 (95% CI 0.74–0.81), a sensitivity of 0.65, and a specificity of 0.77. For the validation cohort, the values were 0.89, 0.92, and 0.78. Thus, the model is not institution specific. The model can be readily accessed in the outpatient clinic. Twelve patients (2.2%) of the AKI group developed ESRD, which leads to irreversible renal damage and a need for lifelong dialysis. The model classified all 12 patients as high risk. Thus, the model will improve long-term prognosis of TKA patients; high-risk patients require risk alleviation. The odds ratio for ESRD development was 9.8 (4.3–22.4) when the AKI and non-AKI groups were compared. Postoperative AKI is, thus, very unsafe; surgeons should strive to avoid it.

Several studies have used machine learning to develop predictive AKI models [14, 17, 18]. However, the limitations include the use of excessive numbers of variables (e.g., 72–93 variables; some of these variables, such as the Braden score, are not measured routinely). An excess of variables compromises external validation (thus far, no model has been externally validated). To use models with high numbers of variables, EMR embedding is required, which is impractical and causes difficulty with respect to use in other institutions. In addition, the models include both intraoperative and postoperative variables; thus, they cannot be used to plan surgery or management. One study claimed an AUC over 0.9 [15], but included the current serum level of creatinine, changes in that level, and length of hospital stay; thus, it predicted AKI after AKI onset or even after patient discharge. Excluding the changes in the serum creatinine level, the AUC fell to 0.72, less than our AUC (0.78). Our model offers more robust prediction than others, but uses only six

Table 2 Comparison of the AKI and non-AKI groups of the developmental cohort,

Characteristics	Developmental cohort (N = 5,302)				
	AKI (*N* = 539, 10.2%)	non-AKI (*N* = 4763)	Total	*p*-value	Odds ratio (95% CI)
Selected key variables					
Sex					
Male	128 (24%)	482 (10%)	610 (12%)	< 0.001	2.8 (2.2–3.4)
Female	411 (76%)	4281 (90%)	4692 (88%)		
ASA class					
1	35 (7%)	721 (16%)	756 (15%)	< 0.001	(Reference)
2	431 (81%)	3641 (79%)	4072 (79%)		
3	65 (12%)	260 (6%)	325 (6%)		2.3 (1.7–3.1)
4	0 (0%)	3 (0%)	3 (0%)		
General anesthesia					
Y	54 (10%)	178 (4%)	232 (4%)	< 0.001	2.9 (2.1–3.9)
N	485 (90%)	4582 (96%)	5067 (96%)		
Use of RAASis					
Y	264 (49%)	1614 (34%)	1878 (35%)	< 0.001	1.9 (1.6–2.2)
N	275 (51%)	3149 (66%)	3424 (65%)		
Use of tranexamic acid					
Y	254 (47%)	3055 (64%)	3309 (62%)	< 0.001	0.5 (0.4–0.6)
N	285 (53%)	1708 (36%)	1993 (38%)		
Creatinine (SD)	1.0 (0.4)	0.7 (0.2)	0.8 (0.2)	< 0.001	0.4 (0.3–0.5)
Unselected variables					
Age (SD)	72.6 (7.4)	70.9 (6.8)	71.1 (6.9)	< 0.001	1.0 (1.0–1.0)
BMI (SD)	27.1 (3.6)	26.8 (3.5)	26.8 (3.5)	0.041	1.0 (1.0–1.0)
Type of surgery					
Unilateral	317 (59%)	2550 (54%)	2867 (54%)	n.s	(Reference)
Staged bilateral	193 (36%)	1949 (41%)	2142 (40%)		0.9 (0.7–1.0)
Contemporaneous bilateral	29 (5%)	264 (6%)	293 (6%)		0.9 (0.6–1.3)
Diabetes mellitus					
Y	188 (35%)	974 (20%)	1162 (22%)	< 0.001	2.1 (1.7–2.5)
N	351 (65%)	3789 (80%)	4140 (78%)		
Use of antithrombotics					
Y	191 (35%)	1159 (24%)	1350 (25%)	< 0.001	1.7 (1.4–2.1)
N	348 (65%)	3604 (76%)	3952 (75%)		
Use of diuretics					
Y	90 (17%)	450 (9%)	540 (10%)	< 0.001	1.9 (1.5–2.5)
N	449 (83%)	4313 (91%)	4762 (90%)		
Use of NSAIDs					
Y	230 (43%)	2080 (44%)	2310 (44%)	n.s	1.0 (0.8–1.2)
N	309 (57%)	2683 (56%)	2992 (56%)		
Use of statins					
Y	203 (38%)	1503 (32%)	1706 (32%)	0.004	1.3 (1.1–1.6)
N	336 (62%)	3260 (68%)	3596 (68%)		
BUN (SD)	21.0 (8.2)	17.2 (5.2)	17.6 (5.7)	< 0.001	0.9 (0.9–0.9)
eGFR (SD)	67.2 (22.4)	82.3 (14.7)	80.8 (16.3)	< 0.001	1.0 (1.0–1.0)
Hemoglobin (SD)	12.6 (1.6)	12.9 (1.2)	12.9 (1.3)	< 0.001	1.2 (1.1–1.3)
Platelets (SD)	238.2 (64.9)	245.2 (61.3)	244.5 (61.7)	0.012	1.0 (1.0–1.0)

**AKI* acute kidney injury, *SD* standard deviation, *ASA class* American Society of Anesthesiologists classification, *RAASis* renin–angiotensin–aldosterone system inhibitors, *BMI* body mass index, *NSAIDs* non-steroidal anti-inflammatory drug, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate

Table 3 Severities of acute kidney injury in the developmental and validation cohorts

AKI stage	Developmental cohort ($N=539$)	Validation cohort ($N=14$)
1	514	14
2	20	0
3	5	0

AKI acute kidney injury

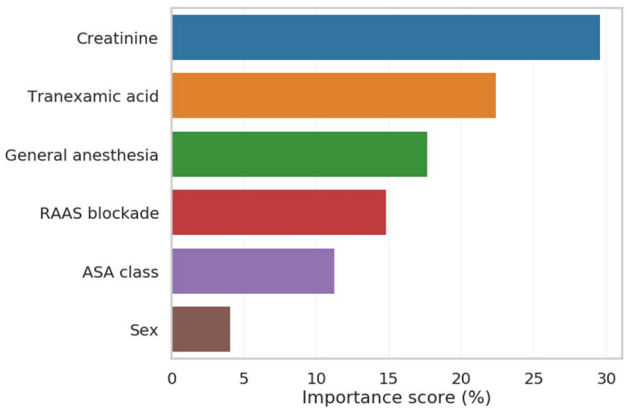

Fig. 3 The feature importance plot of the complete model. *RAASis* renin–angiotensin–aldosterone system inhibitors; *ASA* American Society of Anesthesiologists

variables selected in a sophisticated manner. All six are commonly measured; external validation was simple. Despite differences in the postoperative rehabilitation protocols of the developmental and validation cohorts, our model exhibited high external validation. Thus, this model is suitable for use in other institutions. The developmental cohort was not overfitted. All variables are preoperative. The AKI risk is known when the operation is planned. Measures preventing AKI can be implemented and the operational schedule can be changed.

The preoperative serum level of creatinine is critical in terms of AKI prediction; a higher level indicates greater patient vulnerability, suggesting that poor basal renal function is the most significant risk factor for postoperative AKI, consistent with previous studies [1, 10]. General anesthesia, RAASi use, and male sex were selected as significant predictors; these are known AKI risk factors. The ASA classification is widely used to assess preoperative health; hypertension and diabetes mellitus status are evaluated. ASA class was included because underlying diseases affect renal function. Notably, TXA usage was lower in the AKI group than in the non-AKI group (OR = 0.5). This synthetic anti-fibrinolytic agent is commonly used to prevent and treat bleeding. TXA adversely affects kidney function; however, TXA usage was associated with lower incidences of AKI in both developmental and validation cohorts. TXA reduces hemorrhage, thereby maintaining hemodynamic stability, and is less commonly used in patients with impaired renal function.

Our work had several limitations. First, the AKI incidences in the developmental and validation cohorts were 10.2% and 3.1%, respectively, perhaps because more patients in the validation cohort were prescribed TXA (82% vs. 62%). However, our model exhibited a high AUC in terms of validation cohort predictions, with a very high sensitivity and specificity (0.92 and 0.78, respectively) at the optimal threshold. Although the AKI incidence differed between the two cohorts, the excellent external validation indicates that the model can be used universally. Second, the study cohort included a high proportion of women. In a 2010 study conducted in the USA and a 2008 study conducted in the UK, the proportions of women were 63% [20] and 57% [6], respectively; our proportion was 88%. However, sex was a predictor of AKI in our model. Thus, this model can be applied to populations with various sex ratios. Third, the medication variables were acquired from medical records. Some records might have been missing initially; whereas, some may not have been extracted appropriately by the algorithm. Lastly, because this was a retrospective study, identification of AKI was limited; serum creatinine measurement was performed routinely, but not daily. The exclusion of patients without serum creatinine data might have caused selection bias.

Conclusion

A web-based predictive model for AKI after TKA was developed using a machine-learning algorithm featuring six preoperative variables. The model is simple and has been validated to improve both short- and long-term prognoses of TKA patients. Postoperative AKI may lead to ESRD, which surgeons should strive to avoid.

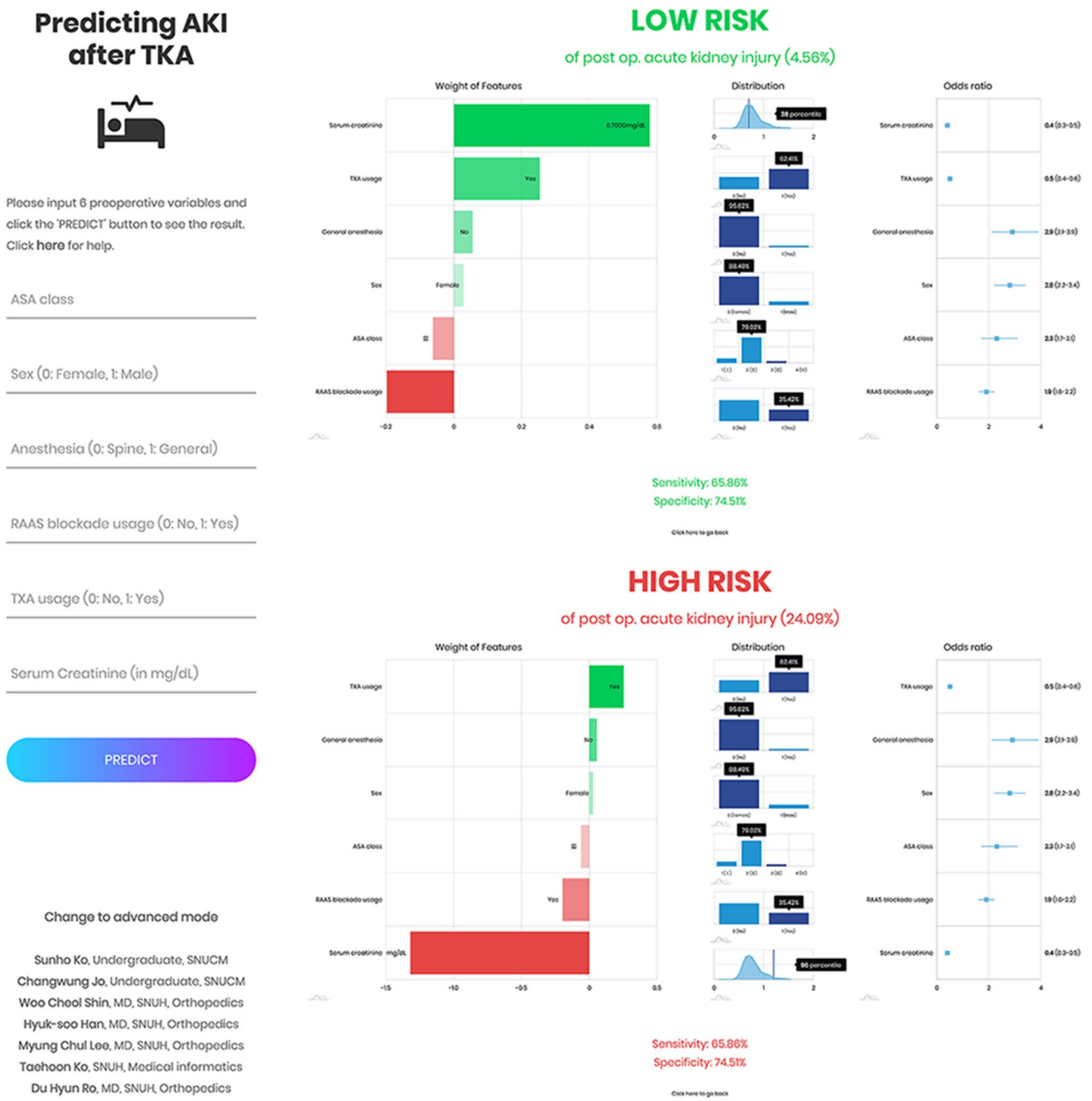

Fig. 4 The web-based risk assessment system (https://safetka.net). Data entry is followed by determination of the risk for acute kidney injury with a display of the extent to which each feature contributed to the prediction

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Compliance with ethical standards

Conflict of interest The authors certify that they have no commercial association that might pose a conflict of interest in connection with this article.

Ethical approval This research was approved by the Institutional Review Board of our institution (IRB No. H-1901-079-1003).

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