의학박사 학위논문

화상 수술 후 90일 사망률에 대한 수술 전 적혈구 크기 분포의 영향

Impact of preoperative red cell distribution width on 90-day mortality after burn surgery

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이 논문을 의학박사 학위 논문으로 제출함

2022년 2월

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ABSTRACT

Background: Severe burns may involve all of the organs which lead to a series of pathophysiological process resulting in mortality. The clinicians are acknowledging the importance of predicting mortality to increase the survival. The pathophysiology of burn is characterized by the inflammatory reaction resulting in serious complication. The red cell distribution width (RDW) is one of the component of complete blood cell count which is recently studied by various medical field for its ability as an indicator of systemic inflammation and as a predictor of mortality. Recently, machine learning model has gained attention for the diagnostic and prognostic performance that automatically build analytical models to predict postoperative mortality. Therefore, the author evaluated the risk factors including RDW that predict mortality in patients after burn surgery and also evaluated the clinical features to establish 90-day mortality prediction model using machine learning technique.

Objective: The author evaluated the RDW and other perioperative characteristics as risk factors for mortality prediction in patients after burn surgery. Also, these risk factors were analyzed using machine learning technique to evaluate the prediction ability of different machine learning models.

Methods: The preoperative clinical features including laboratory findings and basic characteristics of patients were collected. Risk factors for mortality after burn surgery were evaluated using univariate and multivariate logistic regression analyses. In addition, the incidence of postoperative acute kidney injury (AKI) was evaluated. A receiver operating characteristic (ROC) curve analysis of the preoperative RDW was performed. The 90-day mortality rate was analyzed using the Kaplan-Meier survival analysis with a log-rank test to compare the survival rate after the burn surgery. The hazard ratio of mortality in RDW groups by the cutoff value was analyzed using Cox proportional-hazards regression. Also, clinically important features for predicting mortality in patients after burn surgery were selected using a random forest regressor. The author evaluated the area under the ROC curve (AUC) and classifier accuracy to compare the predictive accuracy of prediction by machine learning algorithms including random forest, adaptive boosting, decision tree, linear support vector machine, and logistic regression.

Results: Those who met the inclusion and exclusion criteria were 731 patients. The 90-day mortality of the patients after the burn surgery was 27.1% (198/731). Among the preoperative variables, age [Odds ratio (OR) 1.067; 95% confidence interval (CI) 1.047-1.088], DM (OR 3.211; 95% CI 1.288-8.000), ASA PS III & IV (OR 4.918; 95% CI 1.581-15.305), TBSA burned (OR 1.095; 95% CI 1.078-1.113), RDW (OR 1.679; 95% CI 1.378-2.046), prothrombin time (OR 4.649; 95% CI 1.259-17.171), and creatinine (OR 1.818; 95% CI 1.181-2.798) were considered independent risk factors for mortality in the multivariate logistic regression analysis. Cox proportional hazards regression was used to analyze the mortality, and the hazard ratio after multivariable adjustment was 1.238 (95% CI 1.138-1.347, $p < 0.001$) in the RDW > 12.9 group. In addition, the incidence of postoperative AKI was higher in the non-survivor group than in the survivor group (88, 44.4% vs. 30, 5.6%, $p < 0.001$). As for machine learning model, a total of 11 clinical features were selected using the random forest regressor from the 16 features. The 11 features included were age, ASA PS, TBSA burned, hemoglobin, RDW, platelet, prothrombin time, albumin, creatinine, platelet-lymphocyte ratio, and systemic immune-inflammation index which is calculated by (neutrophil x platelet)/lymphocyte. Of these 11 features, the most significant predictors were TBSA burned (0.28447 ± 0.28447), RDW (0.10053 ± 0.10053), and age (0.08842 ± 0.08842). Random forest showed the highest AUC (0.922 ± 0.020, 95% CI 0.902-0.942) among the other models with sensitivity and specificity of 66.2% and 93.8%, respectively. The pairwise comparisons of the AUC using DeLong's test demonstrated that random forest (AUC = 0.922) showed no statistical difference with adaptive boosting (AUC = 0.915).

Conclusion: This study reveals that preoperative RDW could have the ability to predict 90-day mortality in patients after burn surgery. Furthermore, in patients with high RDW prior to burn surgery, postoperative AKI increases the mortality rate further. Therefore, patients with high RDW before burn surgery should be aware of the development of postoperative AKI. Also, this study demonstrated that the most significant predictors for mortality after burn surgery are TBSA burned, RDW, and age. Random forest showed the best performance for predicting mortality among other models.

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GENERAL INTRODUCTION

Burns are one of the most devastating traumatic injury that causes of morbidity and mortality throughout the world. Burn wounds induce excessive inflammatory response that triggers the immune system to protect against risk of infection which can be detrimental and be fatal.[1] The inflammatory mediators produced and released after burn injury affects microcirculation which results in significant hypovolemic shock and substantial tissue injury.[2] The challenging resuscitation and treatment with further adverse outcomes lead to advance in studies related to predicting risk factors. Early detection with recognition of risk factors associated with mortality may be essential in the management of burn injury.

The extent of injury is described using the percentage of the total body surface area (TBSA) that is affected by a burn. The evaluation of TBSA burned is important during the initial management for estimating fluid requirements. TBSA burned is known to be one of the risk factors of mortality in burn injury since higher TBSA leads to poor prognosis.[3] Age is another well-known risk factor of mortality in burn patients.[4] The underlying medical conditions of the elderly, the impaired response to infection, decreased ability to tolerate stress and physiological insult, and poor nutritional status may influence the adverse outcome of the old aged patients after burn injury.[5-7] Another major risk factor that affects mortality in burn is the presence of inhalation injury. Inhalation injury is reported to be third most important factor in the prediction of mortality in burn patients.[8] Burn injury with flames may accompany inhalation injury with different severity. Since inhalation injury is directly related to airway, the consequences of this injury may be fatal.[9,10]

Several preoperative variables are analyzed for their predictive ability of mortality in burn patients. Complete blood count (CBC) is one of the routinely applied laboratory blood tests for most of the patients. The unique components of CBC are known to be related with inflammation or infection that affects the prognosis of the medical conditions.[11] Of these simple blood biomarker, red cell distribution width (RDW) is a numerical measurement of the range in the volume and size of the erythrocytes. An increase of RDW may reflect conditions that modify erythrocyte shapes as a result of premature release of immature cells into the bloodstream as in case of massive blood loss.[12] In addition, reports have shown that inflammation contributes to an increased RDW by inhibiting the production of erythropoietin or by decreasing erythrocyte survival.[13,14] Recently, RDW has been known to have a prognostic ability to predict morbidity and mortality in various clinical conditions.[15] In burn patients, high RDW was associated with adverse outcomes with mortality but was not an independent risk factor.[16,17] The author sought to investigate the prognostic ability of preoperative RDW as an independent risk factor after burn surgery.

One of the serious and common complication of burn injury is acute kidney injury (AKI).[18] The occurrence of AKI is multifactorial and complicated which usually relates to mortality.[19] Severe burn patients are subjected to aggressive fluid resuscitation which is preceded by extreme volume depletion and this resuscitation is the culprit for intra-abdominal hypertension and abdominal compartment syndrome.[20] This process leads to decreased renal perfusion and inflammation which accelerates renal failure. Studies have investigated on the impact of RDW on prognosis for critically ill patients with AKI or patients with AKI after cardiac surgery.[21,22] However, the association of RDW and AKI in burn patients is not clearly known. Thus, the author attempted to evaluate the impact of RDW in AKI patients.

Machine learning is a subset of artificial intelligence (AI) that develops algorithms and technologies that enable computers to learn. Machine learning is one of the statistical methods for extracting regularity from the data. In machine learning, there are various models or algorithms that extract laws, predict, and classify them. Applications of machine learning have advanced recently in the various aspects of medicine.[23] Logistic regression is a traditional model commonly employed in medical applications to interpret clinical data in depth. On the other hand, the machine learning models recently include random forest (RF), adaptive boosting (AB), decision tree (DT), support vector machine (SVM), and logistic regression (LGR) which are methods to find a more optimal predictive model.[24-27]

In anesthesiology, the applications of this machine learning include depth of anesthesia monitoring, control of anesthesia, event and risk prediction, ultrasound guidance, pain management, and operating room logistics.[28] Machine learning model has gained attention for the diagnostic performance that automatically build analytical models to predict postoperative mortality.[29] Mortality prediction in burn injury is considered crucial in the early management which can affect the outcome of the patients. Studies in machine learning models for mortality prediction in burn injury are in progress since decades ago.[30,31] The application of machine learning in burn injury enables clinicians to reveal and learn the patterns or correlations that was not disclosed by the traditional linear statistical analysis.[32] Not only machine learning for mortality prediction is being studied but also prediction of sepsis and AKI in burn patients is an issue of concern.[33] However, the performance ability of the machine learning on mortality after burn surgery is not clearly elucidated.

In this doctoral thesis, the author sought to evaluate preoperative risk factors including RDW for 90-day mortality in patients after burn surgery. In Chapter 1, the author evaluated preoperative risk factors, including preoperative RDW, for prediction of mortality after burn surgery. The identification of the incidence of postoperative AKI in burned patient and its association with RDW will be discussed. In Chapter 2, the author focused the preoperative clinical features to establish and compare the machine learning techniques for prediction of mortality after burn surgery.

CHAPTER 1

Preoperative red cell distribution width as a prognostic factor

to predict 90-day mortality after burn surgery

1.1. INTRODUCTION

Burn injuries can lead to serious complications that affect almost every organ system and result in significant morbidity and mortality.[34] However, mortality has decreased with the advances in treatments of managing burn patients throughout the world and with vast amount literature based on risk factors and predictors of mortality.[35,36] Thus, the importance of predicting complications of burn injury is being acknowledged by most of the clinicians. One of the serious complication is AKI which is the result of massive fluid loss and inflammation after burn injury. Since the progression of AKI leads to mortality, it is essential to understand the association of this complication with the perioperative variables.

Several biomarkers have been reported which is known to predict mortality in burn patients. After burn injury, systemic inflammatory response eventually results in leukopenia, thrombocytopenia, and coagulopathy.[37] One of the simple blood test to check this response is CBC. Inflammatory markers as a prognostic value include neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and systemic immune- inflammation index (SII) which is easily calculated.[38] Of these simple blood biomarker, RDW has been known to predict morbidity and mortality in various clinical conditions.[15] Traditionally used as a differential diagnosis of anemias, RDW has become a predictor of mortality in cardiovascular and respiratory diseases recently.[39-41] This prognostic value of RDW can also be applied to burn patients.[16,17] In addition, RDW can act as an independent risk factor in predicting acute respiratory distress syndrome after severe burn injury.[42] However, the association of preoperative RDW with mortality in the patients after burn surgery is not clearly known.

Thus, the purpose of the present study was to investigate the predictive value of RDW as a risk factor in 90-day mortality after burn surgery. Also, other preoperative risk factors that affect mortality of the patients after burn surgery have been analyzed.

1.2 METHODS

Study population

Patients admitted to intensive care unit (ICU) before burn surgery from January 2010 to February 2018 were recruited. Data from the first burn surgery were collected for patients who had several burn surgeries. Inclusion criteria were patients administered with second- or third-degree burn who underwent burn surgery within 14 days of burn event. Patients under 18 years old, who underwent local anesthesia, with TBSA burned less than 20%, and with known chronic kidney disease were excluded from the study. We reviewed electronic medical record of these patients to obtain the laboratory and clinical data. This retrospective study was approved by the Institutional Review Board of the Ethical Committee of Hangang Sacred Heart Hospital, Hallym University, Seoul, Korea (No. 2018-057).

Anesthetic and surgical techniques

All patients fasted for 8 hours prior to surgery. In the operating room, patients were monitored with blood pressure, electrocardiography, and pulse oximetry before the induction of general anesthesia. Anesthesia was induced with propofol (1.5-2 mg/kg) and rocuronium (0.6-0.8 mg/kg). Anesthesia was maintained at a fractional inspired oxygen concentration of 0.5 with nitrous oxide combined with sevoflurane (2.0-3.0 vol%) or desflurane (6.0-8.0 vol%). The tidal volume was set to 8-10 mL/kg of ideal body weight, and the respiratory rate was adjusted to maintain an end-tidal CO_2 level of 30-35 mmHg. Fluid administration was controlled according to our institutional protocol based on the mean arterial blood pressure, heart rate, urine output and blood loss. For fluid management, crystalloid was administered at a rate of 6–10 mL/kg/h, and colloid was administered when the blood loss was estimated as >500 mL during the burn surgery. Packed red blood cells (RBC) were transfused to maintain the hemoglobin concentration with ≥ 8 g/dL. The mean blood pressure was controlled to maintain at > 65 mmHg. Types of burn surgeries included escharectomy, fasciotomy, cadaveric skin graft, or split-thickness skin graft. The necrotic burn area was removed up to a possible depth with tangential excision for smaller burns and fascial excision for larger burns according to the burn depth. Deep second- or third-degree burn requires a skin graft such as a temporary cadaveric skin graft or a permanent autograft depending on the burn size and depth.[43]

Data collection

The demographic data, laboratory data, and other variables of the patients were reviewed and collected using the electronic medical record system. Preoperative characteristics of the patients include sex, age, body mass index (BMI), history of hypertension (HTN) or diabetes mellitus (DM), American Society of Anesthesiologists physical status (ASA PS), TBSA burned, and the presence of inhalation injury. TBSA burned refers to any type of burn involving certain percentage of body surface with second- or third-degree burn. The presence of inhalation injury was diagnosed by bronchoscopic finding, which were classified as normal, mild, moderate or severe. Bronchoscopic findings other than normal were considered that inhalation injury is present. All the preoperative blood tests were performed in the early morning on the day of the surgery or on the day before surgery. These preoperative laboratory data include hemoglobin, platelet, prothrombin time, albumin, creatinine, RDW, NLR, PLR, MLR, and SII. NLR, PLR, MLR, and SII were each calculated using the given information of the CBC results. NLR is the ratio between neutrophil and lymphocyte, PLR is the ratio between platelet and lymphocyte, and MLR is the ratio between monocyte and lymphocyte.[44-46] SII was calculated using the following formula: (granulocyte × platelet)/lymphocyte.[47] Duration of anesthesia along with hospital and ICU stay were recorded. In addition, postoperative AKI was investigated according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which is defined by an increase in serum creatinine by 0.3 mg/dL within 48 hours or an increase in serum creatinine to ≥ 1.5 times the baseline within 7 days postoperatively.[48] Daily creatinine levels were checked for 7 consecutive postoperative days for the diagnosis of AKI. The urine output criterion of KDIGO was not used because of inconsistency in the urine output measurement.

Primary and secondary outcomes

The primary endpoint was the analysis of prediction ability of RDW in 90-day mortality after the burn surgery. The secondary endpoint of this study was the identification of the incidence of postoperative AKI in burned patient and its association with preoperative RDW.

Statistical analysis

Patients were divided into non-survivor and survivor groups. All continuous variables were presented as mean ± SD. The variables were analyzed between non-survivor and survivor groups using Student's *t* test or the Mann-Whitney U test, as appropriate. Categorical variables were presented as number (percentage) and were analyzed using chi-square test or Fisher's exact test, as appropriate. Risk factors for 90-day mortality after burn surgery were identified using univariate and multivariate logistic regression analysis. A two-tailed p-values <0.05 were considered statistically significant. The significant factors in univariate logistic regression were analyzed in the backward stepwise elimination procedure of the multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve analysis was used to determine the ability of RDW to predict mortality after burn surgery. The area under the ROC curve (AUC) was calculated by the trapezoid rule. The RDW value with the highest sensitivity and specificity was set as the optimal cut-off value. The 90-day mortality rate was analyzed using the Kaplan-Meier survival analysis with a log-rank test to compare the survival rate after the burn surgery between the two groups. In addition, hazard ratio of mortality in RDW groups by the cutoff value was analyzed using Cox proportional-hazards regression. All statistical analyses were performed with SPSS for Windows (version 24.0; IBM-SPSS Inc., Armonk, NY, USA).

1.3 RESULTS

Study population

A total population of 1488 patients were admitted to the ICU before burn surgery. Those who met the inclusion and exclusion criteria were 731 patients (Figure 1.1). The 90-day mortality of the patients after the burn surgery was 27.1% (198/731).

Primary outcome

There were no statistically significant differences with regard to sex, body mass index, hemoglobin, NLR, PLR, MLR, and SII (Table 1.1). The age and TBSA burned (%) were significantly higher in the non-survivor group than in the survivor group ($p < 0.001$ for both). Also, the number of patients with DM ($p < 0.001$), HTN ($p = 0.003$), and inhalation injury ($p < 0.001$) were higher in the non-survivor group than in the survivor group. For the laboratory findings, platelet count, prothrombin time, RDW, albumin, and creatinine showed significant difference between the two groups. Univariate logistic regression analysis identified that age, DM, HTN, ASA PS III & IV, TBSA burned, inhalation injury, RDW, platelet, prothrombin time, albumin, and creatinine were significantly associated with 90-day mortality of patients after burn surgery (Table 1.2). Of these factors, age [Odds ratio (OR) 1.067; 95% confidence interval (CI) 1.047-1.088], DM (OR 3.211; 95% CI 1.288-8.000), ASA PS III & IV (OR 4.918; 95% CI 1.581-15.305), TBSA burned (OR 1.095; 95% CI 1.078-1.113), RDW (OR 1.679; 95% CI 1.378-2.046), prothrombin time (OR 4.649; 95% CI 1.259-17.171), and creatinine (OR 1.818; 95% CI 1.181-2.798) were considered independent risk factors for mortality in the multivariate logistic regression analysis.

Figure 1.2 shows the ROC curve analysis for the preoperative RDW for prediction of mortality after burn surgery. The AUC was 0.701 with an optimal cutoff value of 12.9, sensitivity of 73.7 %, and specificity of 58.0 %. The patients were divided into two groups according to the cut-off value of RDW for the Kaplan-Meier survival analysis. Table 1.3 demonstrates the comparison of baseline characteristics and laboratory findings between RDW ≤ 12.9 group ($n = 361$) and RDW > 12.9 group (n = 370). Among the collected variables, age, sex, DM, TBSA burned, inhalation injury, hemoglobin, RDW, prothrombin time, albumin, creatinine, NLR, PLR, and SII showed significant difference between the two groups. Cox proportional hazards regression was used to analyze the mortality, and the hazard ratio after multivariable adjustment was 1.238 (95% CI 1.138-1.347, $p < 0.001$) in the RDW > 12.9 group (Table 1.4). The variables used for multivariate adjustment were age, DM, HTN, ASA PS, TBSA burned, inhalation injury, platelet, prothrombin time, albumin, creatinine, and RDW. The survival probability of the group with RDW ≤ 12.9 was 85.6% and the group with RDW > 12.9 was 61.1% on day 90 (Figure 1.3). Also, ICU stay, postoperative incidence of AKI, and 90-day mortality were significantly different between the two groups (Table 1.5).

Figure 1.1. Flow diagram of the study participants. ICU, intensive care unit. TBSA, total body surface area.

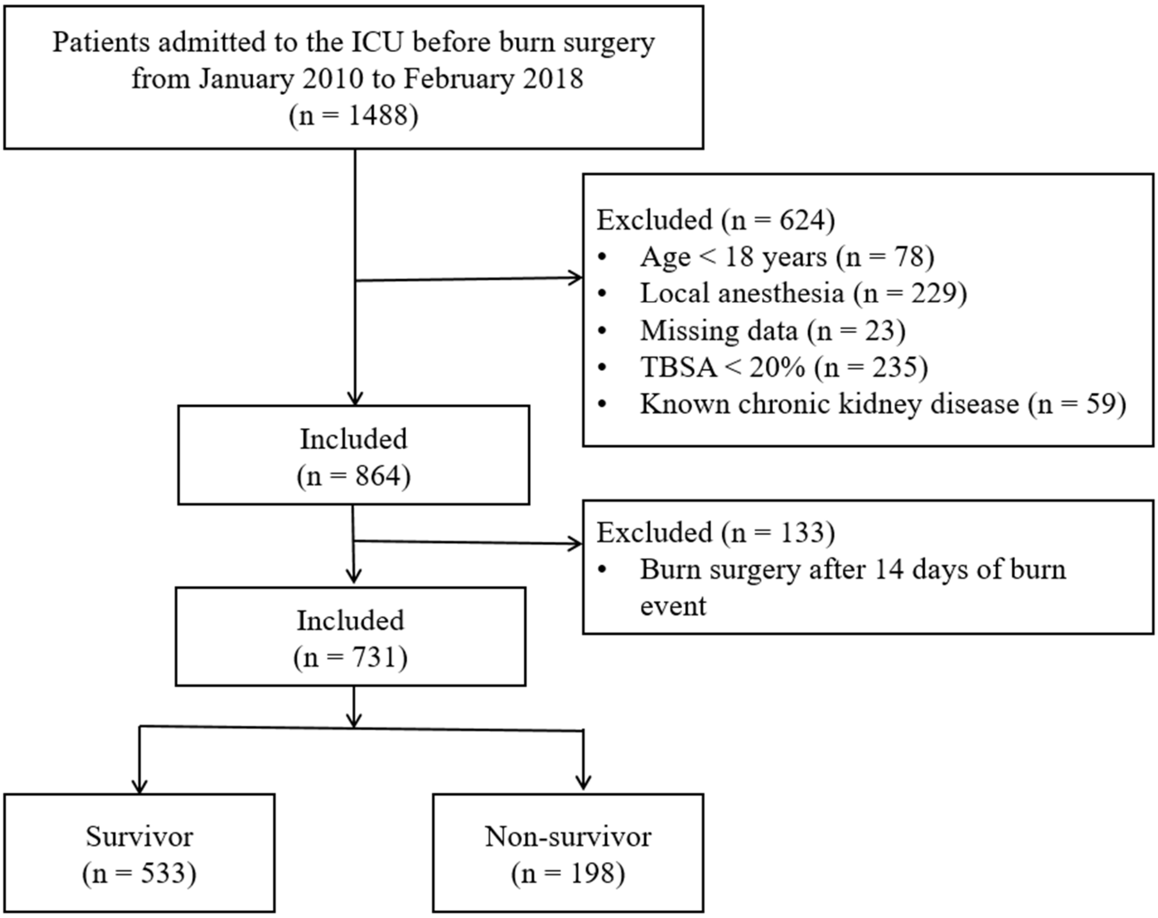


Table 1.1. Baseline characteristics and laboratory findings of the survivor and non-survivor group

Variables	**Survivor group (n = 533)**	**Non-survivor group (n = 198)**	**p-value**
Age, yr	52.0 ± 14.4	58.0 ± 15.9	<0.001
Sex, male/female	441 (82.7)/92 (17.3)	166 (83.8)/32 (16.2)	0.825
Body mass index, kg/m^2	23.6 ± 3.4	23.5 ± 3.1	0.765
Diabetes mellitus	22 (4.1)	26 (13.1)	<0.001
Hypertension	72 (13.5)	45 (22.7)	0.003
ASA PS			<0.001
I	71 (13.3)	6 (3.0)	
II	240 (45.0)	26 (13.1)	
III & IV	222 (41.7)	166 (83.8)	
TBSA burned, %	38.5 ± 15.1	63.6 ± 20.7	<0.001
Inhalation injury	165 (31.0)	110 (55.6)	<0.001
Hemoglobin, g/dL	13.5 ± 3.0	13.9 ± 3.5	0.100
RDW	13.0 ± 1.0	13.8 ± 1.4	<0.001
Platelet count, $\times 10^9$/L	204.8 ± 111.3	180.5 ± 133.8	0.023
Prothrombin time, INR	1.1 ± 0.2	1.2 ± 0.3	<0.001
Albumin, g/dL	2.9 ± 0.8	2.5 ± 0.9	<0.001
Creatinine, mg/dL	0.78 ± 0.42	1.02 ± 0.62	<0.001
NLR	10.6 ± 19.1	11.2 ± 15.7	0.695
PLR	276 ± 464	304 ± 606	0.553
MLR	0.85 ± 1.31	1.13 ± 2.39	0.121
SII	2171 ± 4108	1909 ± 3783	0.435

Data are shown as mean ± standard deviation or number (%) as appropriate. ASA PS, American Society of Anesthesiologists physical status; TBSA, total body surface area; RDW, red cell distribution width; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune inflammation index.

Table 1.2. Univariate and multivariate analyses for evaluating the risk factors of mortality after burn surgery

	Univariate analysis		**Multivariate analysis**	
Variables	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age, yr	1.027 (1.016–1.039)	<0.001	1.067 (1.047–1.088)	<0.001
Diabetes mellitus	3.511 (1.940–6.356)	<0.001	3.211 (1.288–8.000)	0.012
Hypertension	1.883 (1.244–2.852)	0.003	1.348 (0.683–2.660)	0.389
ASA PS				
I	1.000 (Reference)		1.000 (Reference)	
II	1.282 (0.508–3.237)	0.599	1.101 (0.329–3.681)	0.876
III & IV	8.848 (3.755–20.852)	<0.001	4.918 (1.581–15.305)	0.006
TBSA burned, %	1.075 (1.063–1.087)	<0.001	1.095 (1.078–1.113)	<0.001
Inhalation injury	2.788 (1.994–3.898)	<0.001	1.380 (0.844–2.257)	0.199
Hemoglobin, g/dL	1.048 (0.995–1.104)	0.075		
RDW	1.711 (1.471–1.990)	<0.001	1.679 (1.378–2.046)	<0.001
Platelet count, $\times 10^9$/L	0.998 (0.997–1.000)	0.014	0.999 (0.997–1.001)	0.477
Prothrombin time, INR	29.531 (10.480–83.213)	<0.001	4.649 (1.259–17.171)	0.021
Albumin, g/dL	0.596 (0.480–0.741)	<0.001	0.981 (0.686–1.404)	0.916
Creatinine, mg/dL	2.894 (1.908–4.391)	<0.001	1.818 (1.181–2.798)	0.007
NLR	1.002 (0.993–1.010)	0.696		
PLR	1.000 (1.000–1.000)	0.506		
MLR	1.090 (0.994–1.195)	0.068		
SII	1.000 (1.000–1.000)	0.440		

CI, confidence interval; ASA PS, American Society of Anesthesiologists physical status; TBSA, total body surface area; RDW, red cell distribution width; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; INR, international normalized ratio.

Figure 1.2. Receiver operating characteristics (ROC) curve analysis of preoperative red cell distribution width (RDW) for prediction of mortality after burn surgery. ROC curve was used to determine the cut-off value of RDW which was 12.9. The area under the ROC curve (AUC) was 0.701.

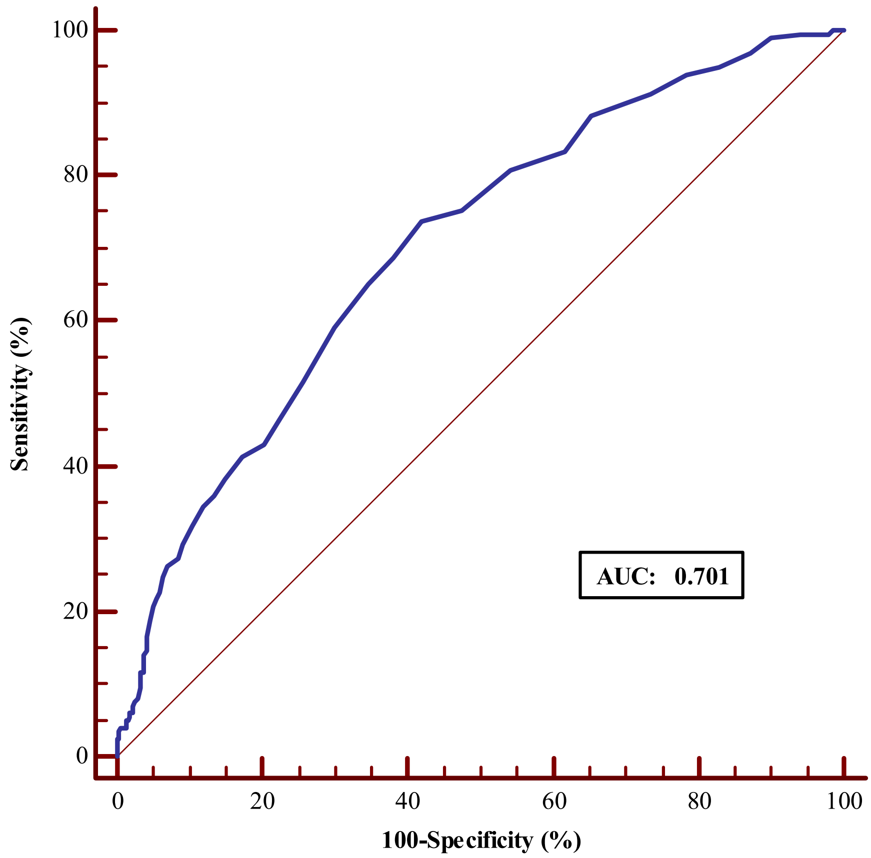


Table 1.3. Baseline characteristics and laboratory findings of RDW ≤ 12.9 and RDW > 12.9 group

Variables	**RDW ≤ 12.9 (n = 361)**	**RDW > 12.9 (n = 370)**	**p-value**
Age, yr	50.7 ± 14.7	56.5 ± 14.8	<0.001
Sex, male/female	311 (86.1)/50 (13.9)	296 (80.0)/74 (20.0)	0.03
Body mass index, kg/m^2	23.6 ± 3.5	23.5 ± 3.2	0.623
Diabetes mellitus	11 (3.0)	37 (10.0)	<0.001
Hypertension	49 (13.6)	68 (18.4)	0.086
ASA PS			0.025
I	47 (13.0)	30 (8.1)	
II	138 (38.2)	128 (34.6)	
III & IV	176 (48.8)	212 (57.3)	
TBSA burned, %	42.1 ± 18.5	48.5 ± 21.2	<0.001
Inhalation injury	114 (31.6)	161 (43.5)	<0.001
Hemoglobin, g/dL	14.2 ± 2.8	12.9 ± 3.3	<0.001
Platelet count, $\times 10^9$/L	199.5 ± 104.5	196.9 ± 130.3	0.764
Prothrombin time, INR	1.1 ± 0.2	1.2 ± 0.3	<0.001
Albumin, g/dL	2.9 ± 0.8	2.7 ± 0.8	0.001
Creatinine, mg/dL	0.77 ± 0.25	0.92 ± 0.64	<0.001
NLR	8.2 ± 9.3	13.3 ± 23.6	<0.001
PLR	247 ± 386	320 ± 598	0.05
MLR	0.84 ± 1.13	1.01 ± 2.08	0.174
SII	1683 ± 2872	2507 ± 4859	0.005

Data are shown as mean ± standard deviation or number (%) as appropriate. ASA PS, American Society of Anesthesiologists physical status; TBSA, total body surface area; RDW, red cell distribution width; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index.

Table 1.4. Hazard ratio of mortality in patients with RDW ≤ 12.9 and RDW > 12.9.

			Crude		**Multivariable adjusted**	
			HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
90-day mortality	RDW ≤ 12.9	n=361	1 (reference)		1 (reference)	
	RDW > 12.9	n=370	1.327 (1.239-1.422)	< 0.001	1.238 (1.138-1.347)	<0.001

* Multivariate analysis adjusted for age, diabetes mellitus, hypertension, American Society of Anesthesiologist physical status, total body surface area burned, inhalation injury, platelet, prothrombin time, albumin, creatinine, and red cell distribution width. HR, hazard ratio; CI, confidence interval; and RDW, red cell distribution width.

Figure 1.3. Kaplan-Meier curve of 90-day survival of the patients after the burn surgery. The green line (solid) indicates the group with RDW ≤ 12.9 and the orange line (dotted) indicates the group with RDW > 12.9.

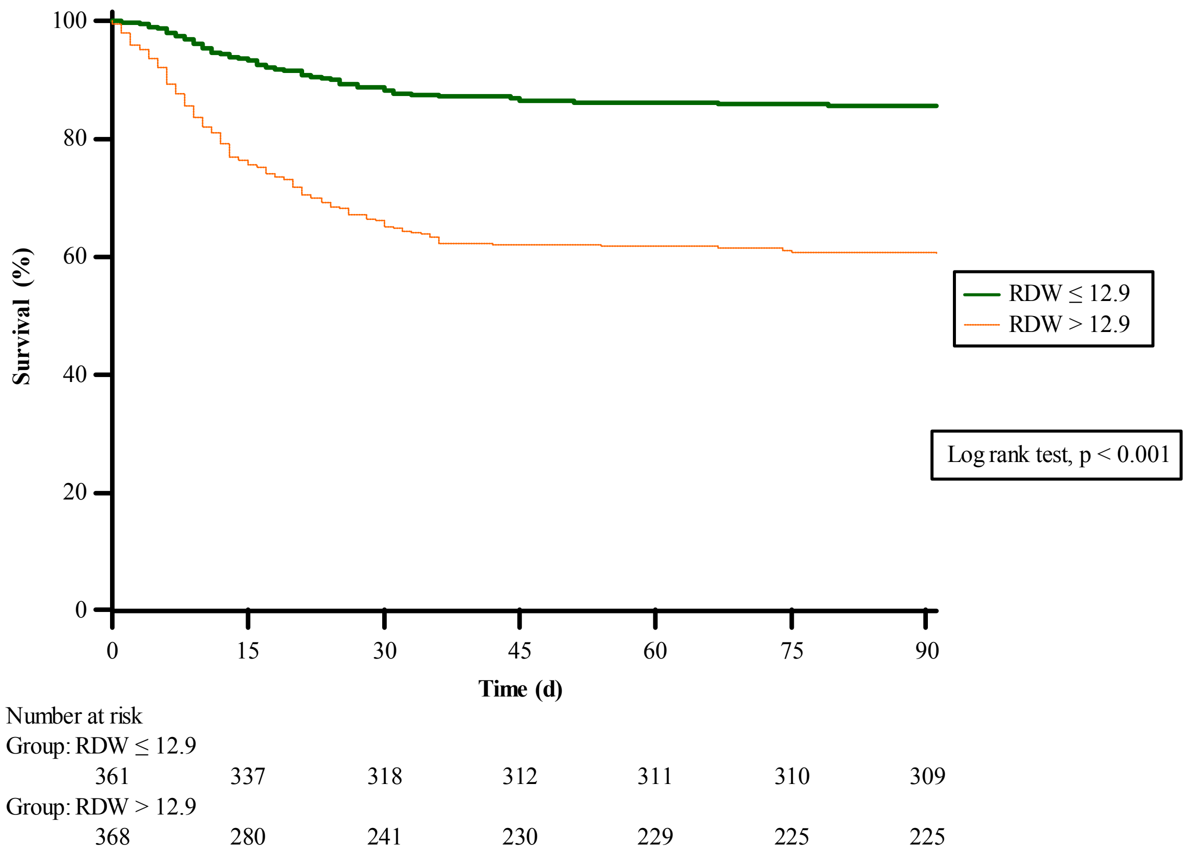


Table 1.5. Intraoperative and postoperative characteristics of RDW ≤ 12.9 and RDW > 12.9 group

Variables	**RDW ≤ 12.9 (n = 361)**	**RDW > 12.9 (n = 370)**	**p-value**
Duration of anesthesia, min	142.6 ± 50.7	145.0 ± 53.9	0.530
Hospital stay, day	60.1 ± 35.1	55.6 ± 44.8	0.139
ICU stay, day	23.3 ± 17.1	30.7 ± 27.2	<0.001
Postoperative AKI	31 (8.6)	87 (23.5)	<0.001
90-day mortality	52 (14.4)	146 (39.5)	<0.001

Data are shown as mean ± standard deviation or number (%) as appropriate. RDW, red cell distribution width; ICU, intensive care unit; and AKI, acute kidney injury.

Secondary outcome

In addition, the incidence of postoperative AKI was higher in the non-survivor group than in the survivor group (88, 44.4% vs. 30, 5.6%, $p < 0.001$). The duration of anesthesia showed no significant difference between the two groups ($p = 0.844$). The hospital stay was 71.4 ± 37.5 days for the survivor group and 21.2 ± 19.9 days for the non-survivor group ($p < 0.001$). The ICU stay was 29.1 ± 23.8 days for the survivor group and 21.4 ± 19.6 days for the non-survivor group ($p < 0.001$) (Table 1.6).

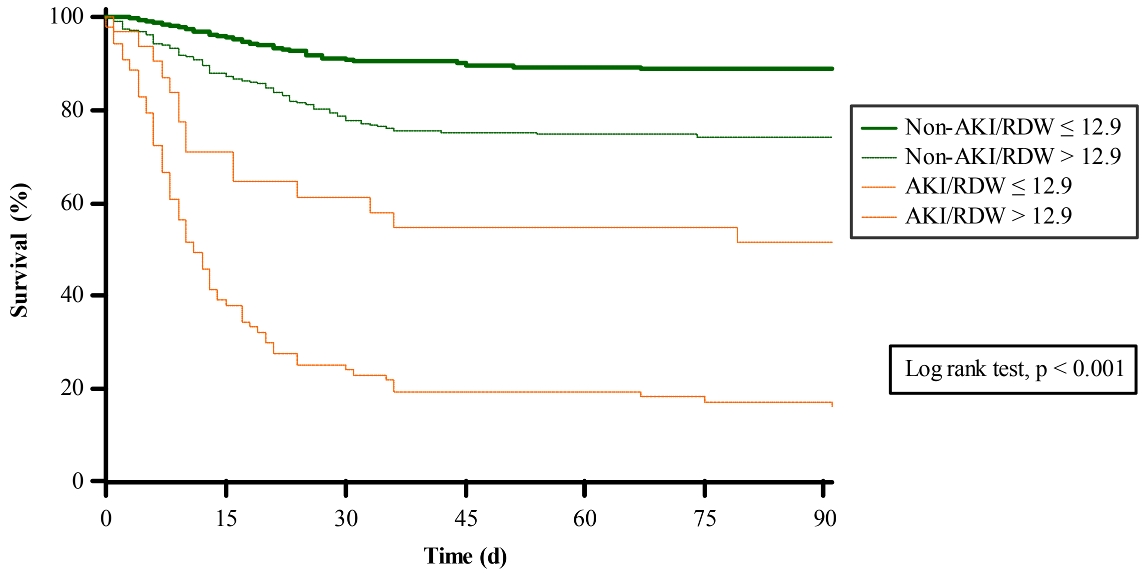
Subgroup analysis according to postoperative AKI showed that the survival rate on day 90 was 88.8%, 74.2%, 51.6%, and 17.6% for the groups of non-AKI with RDW ≤ 12.9, non-AKI with RDW > 12.9, AKI with RDW ≤ 12.9, and AKI with RDW > 12.9 (log rank test, $p < 0.001$) (Figure 1.4).

Table 1.6. Intraoperative and postoperative characteristics of survivor and non-survivor group

Variables	Survivor group (n=533)	Non-survivor group (n=198)	p-value
Duration of anesthesia, min	144.5 ± 51.9	143.6 ± 52.6	0.844
Hospital stay, day	71.4 ± 37.5	21.2 ± 19.9	<0.001
ICU stay, day	29.1 ± 23.8	21.4 ± 19.6	<0.001
Postoperative AKI	30 (5.6)	88 (44.4)	<0.001

Data are shown as mean ± standard deviation or number (%) as appropriate. ICU, intensive care unit; and AKI, acute kidney injury.

Figure 1.4. Kaplan-Meier curve of 90-day survival of the patients with and without AKI after the burn surgery. The green solid line indicates the group with no AKI and RDW ≤ 12.9 which had the best survival probability among the other groups. AKI, acute kidney injury; RDW, red cell distribution width.



Number at risk

Group: Non-AKI/RDW ≤ 12.9						
330	315	299	295	294	293	293
Group: Non-AKI/RDW > 12.9						
283	247	220	213	212	210	210
Group: AKI/RDW ≤ 12.9						
31	22	19	17	17	17	16
Group: AKI/RDW > 12.9						
85	33	21	17	17	15	15

1.4 DISCUSSION

The present study demonstrates that age, DM, ASA PS III & IV, TBSA burned, RDW, prothrombin time, and creatinine were independent risk factors for mortality in patients after burn surgery. Especially, the novel finding of the present study is that RDW was considered significant predictor of mortality in patients after burn surgery. Interestingly, as with the survival analysis based on the subgroups of AKI and RDW, patients with AKI and RDW > 12.9 had the lowest survival rate on day 90. Also, high RDW group was associated with 1.24 higher risk of mortality than the low RDW group.

Burn injury involves with intricate mechanisms of pathophysiology which makes the management of these patients challenging at times.[49] One of these mechanisms include microvascular dysfunction which leads to immunosuppressed state which is susceptible to multiple organ failure and mortality.[50] Many different types of blood cells are involved in this series of burn-induced systemic inflammatory reaction. The prognostic value of blood parameters of CBC such as NLR, MLR, and PLR in burn patients have been studied.[11] Since NLR is considered a marker for inflammation, it is a novel marker for mortality in critically-ill patients.[51] Non-survivors had significantly higher NLR and RDW compared to survivors in burn patients admitted to ICU.[11] However, not all of our study results were in accordance with the previous reports since we evaluated the mortality after the burn surgery. Regarding SII, it is known to have a better prognostic results than NLR or PLR in colorectal cancer patients after the surgery.[52] These inflammatory markers are composites of blood components that are standard, low-cost measurements that are already used in our daily clinical practice and can be easily calculated. Recently, these markers are considered to be more specific than C-reactive protein or erythrocyte sedimentation rate.[38] However, the present results in our study revealed that these factors may not be correlated with mortality after burn surgery.

Age, TBSA, DM, and prothrombin time, and creatinine are known to be risk factors for multiple organ failure and mortality after burn injury which adhere to our results.[53-55] The evaluation of

TBSA burned is important during the initial management for estimating fluid requirements. TBSA burned is known to be one of the risk factors of mortality in burn injury since higher TBSA leads to poor prognosis.[3] Age is another well-known risk factor of morality in burn patients.[4] The underlying medical conditions of the elderly, the impaired response to infection, decreased ability to tolerate stress and physiological insult, and poor nutritional status may influence the adverse outcome of the old aged patients after burn injury.[5-7] Another major risk factor that affects mortality in burn is the presence of inhalation injury. Inhalation injury is reported to be third most important factor in the prediction of mortality in burn patients.[8] Burn injury with flames may accompany inhalation injury with different severity. Since inhalation injury is directly related to airway, the consequences of this injury may be fatal.[9,10] Also, other studies claim survivors have longer hospital stay due to additional treatments.[56] However, the present study results show that non-survivors had a shorter hospital stay which can be explained by the high mortality rate within 90 days.

RDW is used to evaluate the size variability of circulating RBCs and is routinely reported as a component of CBC. The size of the RBCs varies from 80 to 100fL in the blood in normal conditions. However, in certain conditions, RBCs are increased or decreased caused by ineffective RBC production, increased RBC destruction, or blood transfusion. Consequently, the changes of erythrocyte homeostasis eventually result in extensive RBC size heterogeneity, depicted as elevated RDW, which indicate pathologic conditions.[57] Also, these pathologic conditions lead to alterations of osmolality which decrease the ability of RBCs to deform which also is reflected on the RDW level. The pathophysiology of the relationship between RDW and mortality is not clear, but the inflammation cytokines, microvascular alterations, and oxidative stress is thought to be related.[58-60] The relationship of RDW with mortality in critically-ill patients has been reported in various clinical conditions. There is an association between RDW and mortality in pulmonary embolism patients.[61,62] Also, increasing RDW levels have higher mortality rate in these patients.[41,63] RDW was also an independent predictor of mortality in heart failure.[64] In patients with sepsis, non-survivors have higher RDW values compared with survivors.[58] Specifically, RDW is an independent predictor of mortality in patients with gram-negative bacteremia.[65] Also, RDW was predictive of mortality in trauma patients.[66] In burn injury, RDW was significantly elevated in non-survivors during the first week of burn injury.[11,67] RDW is also known to be an independent risk factor in prediction of acute respiratory distress syndrome after severe burn.[42] In this study, RDW was a strong predictor of mortality after the surgery in burn patients.

When the patients were divided into the groups based on the cutoff value of RDW, the higher RDW group significantly had older age; increased incidence of DM and inhalation injury; higher TBSA burned; decreased hemoglobin and albumin; and increased prothrombin time, creatinine, NLR, and SII. Also in postoperative clinical features, ICU stay was longer, and the incidence of postoperative AKI was higher in the higher RDW group. The 90-day mortality was 1.24-fold higher in high RDW group than low RDW group, as validated by the Cox proportional hazards model after adjustment.

AKI is devastating complication which eventually leads to increase in mortality in burn patients.[18,68,69] Studies have demonstrated associations between AKI and RDW with their impact on mortality.[21,22,70] Based on this fact, we have divided the patients into 4 subgroups according to the cutoff value of preoperative RDW and the presence of postoperative AKI. The cut-off value of RDW for mortality in our study was 12.9. The present study found that patients with AKI and RDW > 12.9 have the lowest survival rate which is one-fifth survival rate of the those with no AKI and RDW ≤ 12.9. This suggests that efforts to prevent the occurrence of postoperative AKI in burn patients with high RDW are necessary because the mortality rate is higher if AKI develops postoperatively in patients with a preoperative RDW > 12.9. Follow-up studies are needed to prove this. Though the underlying mechanism between RDW and AKI has not been elucidated, inflammatory reactions and oxidative stress of AKI are reflected by RDW values. Furthermore, in AKI, the renin-angiotensin system promotes the release of erythropoietin and lead to excessive erythropoiesis with increased heterogeneity of RBCs.[71,72]

However, there are some limitations that should be mentioned in our study. First, the nature of its retrospective design has resulted in inevitable missing or inaccurate data. All of the data were based on the electronic medical record which may cause bias with the recorder. Second, although this is a single-center analysis of the burn patients, perioperative clinical management in this eight-year study might have changed over time. Thus, the participants were not representatives of the general population. Third, since only preoperative RDW value was analyzed for mortality at 90 days after surgery, the prediction ability of the RDW values with the mortality cannot be applied to different time points throughout the hospital stay. Lastly, this study did not investigate whether the high mortality predicted by high preoperative RDW is related to complications other than postoperative AKI. Therefore, it cannot be excluded that mortality related to other complications after surgery other than high preoperative RDW before surgery may be higher. All intraoperative data including volume management were not evaluated in this study. However, since the data of the present study were collected in the largest burn center in Asia, which performs standardized burn surgery, these effects on the present outcome may be scarce. Also, all intraoperative data including volume management were not evaluated in this study. These limitations should be taken into account for further studies.

1.5 CONCLUSION

This study reveals that preoperative RDW could have the ability to predict 90-day mortality in patients after burn surgery. The 90-day mortality was 1.24-fold higher in high RDW group than low RDW group. Furthermore, in patients with high RDW prior to burn surgery, postoperative AKI increases the mortality rate further. Therefore, patients with high RDW before burn surgery should be aware of the development of postoperative AKI. The potential risk factors should be considered in the overall management and treatment of the burn patients after the surgery.

CHAPTER 2

Prediction of mortality after burn surgery using machine learning models

2.1 INTRODUCTION

AI has been advanced to medical field including clinical practice of anesthesiology.[28] Machine learning technique is one of the subordinate categories of AI which have advanced as a new trend that leads to a superior prediction ability compared with conventional models.[29] Machine learning model has gained attention for the diagnostic performance which automatically build analytical models to predict postoperative mortality.[73]

Severe burn injuries yield to morbidity and mortality which results from consequences of systemic complications and multiple organ failure.[74] Burn injury triggers systemic inflammatory response in the process of pathophysiology which can be detected by several inflammatory markers.[75] Among the various inflammatory markers, indices of CBC are widely used laboratory tests for early detection of inflammation. RDW has been known to be related to mortality in cardiovascular diseases, respiratory diseases, hepatitis, and septic conditions.[41,58,76-78] Associations between these inflammatory factors and mortality in burn patients after surgery are continuously being reported.[11]

In burn patients, efforts have been made to reveal the potential prediction ability of mortality using machine learning in various approaches.[79,80] Thus, the study aim was to identify the machine learning models with the best diagnostic performance for predicting mortality in patients after burn surgery and to compare each machine learning models. Machine learning models including RF, AB, DT, SVM, and LGR were used in our analysis. This study may be a part for validating machine learning systems in order to adopt machine learning applications into clinical practice.

2.2 METHODS

Study population and data collection

This retrospective study was approved by the Institutional Review Board of the Ethical Committee of Hangang Sacred Heart Hospital, Hallym University, Seoul, Korea (No. 2018-057). Adult patients (≥ 18 years old) who underwent burn surgery under general anesthesia from January 2010 to February 2018 were included. Also, patients who were admitted to the intensive care unit with TBSA burned ≥ 20% were included. We reviewed the electronic medical record to obtain the laboratory and clinical data. The primary outcome was 90-day mortality after burn surgery. The secondary outcome was the selection of the machine learning models which fit the best performance for the prediction of mortality in patients after burn surgery.

The clinical features used for analysis include age, diabetes mellitus, hypertension, ASA PS, TBSA burned, inhalation injury, hemoglobin, RDW, platelet, prothrombin time, albumin, creatinine, NLR, PLR, MLR, and SII. SII is calculated by (neutrophil × platelet)/lymphocyte. The analysis was used with the clinical laboratory findings one day before the surgery. The included patients underwent surgery within 14 days after the burn injury. These features were used as risk factors to be analyzed in the univariate and multivariate logistic regression in Chapter 1.

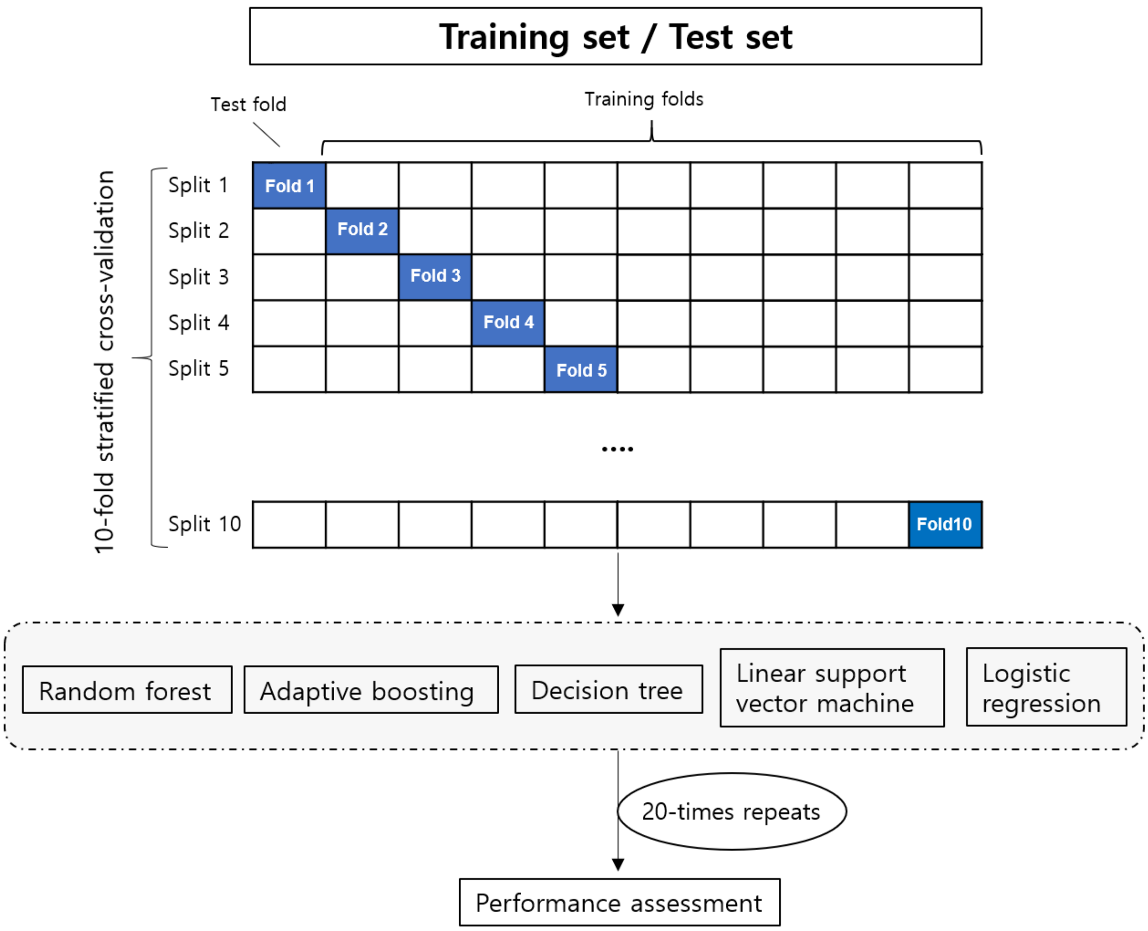
Anesthetic and surgical techniques

All patients fasted for 8 hours prior to surgery. In the operating room, patients were monitored with blood pressure, electrocardiography, and pulse oximetry before the induction of general anesthesia. Anesthesia was induced with propofol (1.5-2 mg/kg) and rocuronium (0.6-0.8 mg/kg). Anesthesia was maintained at a fractional inspired oxygen concentration of 0.5 with nitrous oxide combined with sevoflurane (2.0-3.0 vol%) or desflurane (6.0-8.0 vol%). The tidal volume was set to 8-10 mL/kg of ideal body weight, and the respiratory rate was adjusted to maintain an end-tidal CO_2 level of 30-35 mmHg. During the surgery, volume status was managed using mean arterial blood pressure, heart rate, urine output, and blood loss when necessary. Types of burn surgeries included fasciotomy, cadaveric skin graft, or split-thickness skin graft.

Clinical feature selection and classification method using machine learning

Although many quantitative features can be extracted from medical datasets, these may be highly correlated with each other or simply considered as noise. Thus, it is important to reduce features to select a subset of specific features, enhance the performance, and minimize the computational cost. The feature selection using random forest regressor and the 20 repeated 10-fold stratified cross-validations were performed to avoid overfitting in limited datasets (Figure 2.1).[81] Among the clinical features, important features for predicting mortality in patients after burn surgery were selected using a random forest regressor in Python (Python Software Foundation, version 3.7.4) with the Scikit-learn package (https://github.com/scikit-learn/scikit-learn). A random forest classifier model was trained to use these important features to predict mortality.[82] We evaluated using the ROC curve analysis and classifier accuracy to compare the predictive accuracy of prediction by machine learning algorithms including RF, AB, DT, SVM, and LGR. Statistical differences in the AUC according to each classifier were compared using a machine learning model with Delong's test using open-source R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered statistically significant.

Figure 2.1. 20 repeated 10-fold stratified cross-validation of training set and test set.



Algorithms of each machine learning models

RF is an ensemble of many decision trees which are non-linear models on various sub-samples of the dataset and calculate averaging to improve the predictive accuracy and prevent over-fitting.[82] The importance of each feature is computed from Scikit-learn package of Random Forest. It is also known as the Gini importance.

$$\mathrm{G}(N_j) = \sum_{i=1}^{K} p_i(1-p_i) = 1 - \sum_{i=1}^{K} p_i^2$$

K is the total of class and P is the probability of each class.

The AB algorithms classifier is a meta estimator fitting a classifier on the original dataset and then fitting additional copies of the classifier on the same dataset but where the weights of incorrectly classified instances are adjusted such that subsequent classifiers focus more on difficult cases.[83] It is also calculated as following:

$$\mathrm{h}_f(\mathrm{x}) = \begin{cases} 1, & if \sum_{t=1}^{T} (\log 1/\beta_t) h_t(x) \geq \frac{1}{2} \sum_{t=1}^{T} \log \frac{1}{\beta_t} \\ 0, & otherwise \end{cases}$$

DTs are a non-parametric supervised learning method for classification and regression. The goal of this method is to generate a model predicting a target value by learning simple decision rules inferred from the data features.[84] A tree can be seen as a piecewise constant approximation. For classification outcome taking on values 0,1, …, K-1, for node,

$$P_{mk} = {}^{1}/_{N_m} \sum_{y \in Q_m} I(y = k)$$

be the proportion of class k observations in node *m*. If *m* is a terminal node, predicted probability for this region is set to P_{mk}.

SVM constructs hyperplanes in a high or infinite dimensional space, which can be used for classification, regression or other tasks. Intuitively, a good separation is achieved by the hyperplane that has the maximum gap to the nearest training data points of any class, since in general the larger the margin the lower the generalization error of the classifier.[85,86] The primal problem can be equivalently formulated as:

$$LinearSVR = \; min_{w,b}\frac{1}{2}w^T w + C\sum_{i=1} \max(0, | \; y_i - (w^T \emptyset(x_i) + b)| - \; \varepsilon,$$

where we make use of the epsilon-insensitive loss, i.e. errors of less than are ignored. This is the form that is directly optimized by linear support vector regression (SVR).

LGR is a linear model for classification rather than regression. It quantifies the relationship between a dependent categorical outcome and one or more independent predictor variables. This implementation can fit binary, One-vs-Rest, or multinomial logistic regression with optional, l_1, l_2.[87,88] As an optimization problem, binary class l_1 penalized logistic regression minimizes the following cost function:

$$min_{w,c}\frac{1}{2}w^T w + C\sum_{i=1}^{n} \log(\exp\left(-y_i\left(X_i^T w + c\right)\right) + 1)$$

Similarly, l_2 regularized logistic regression solves the following optimization problem:

$$min_{w,c}\|w\|_1 + C\sum_{i=1}^{n} \log(\exp\left(-y_i\left(X_i^T w + c\right)\right) + 1)$$

2.3 RESULTS

Basic demographics and selected important clinical features

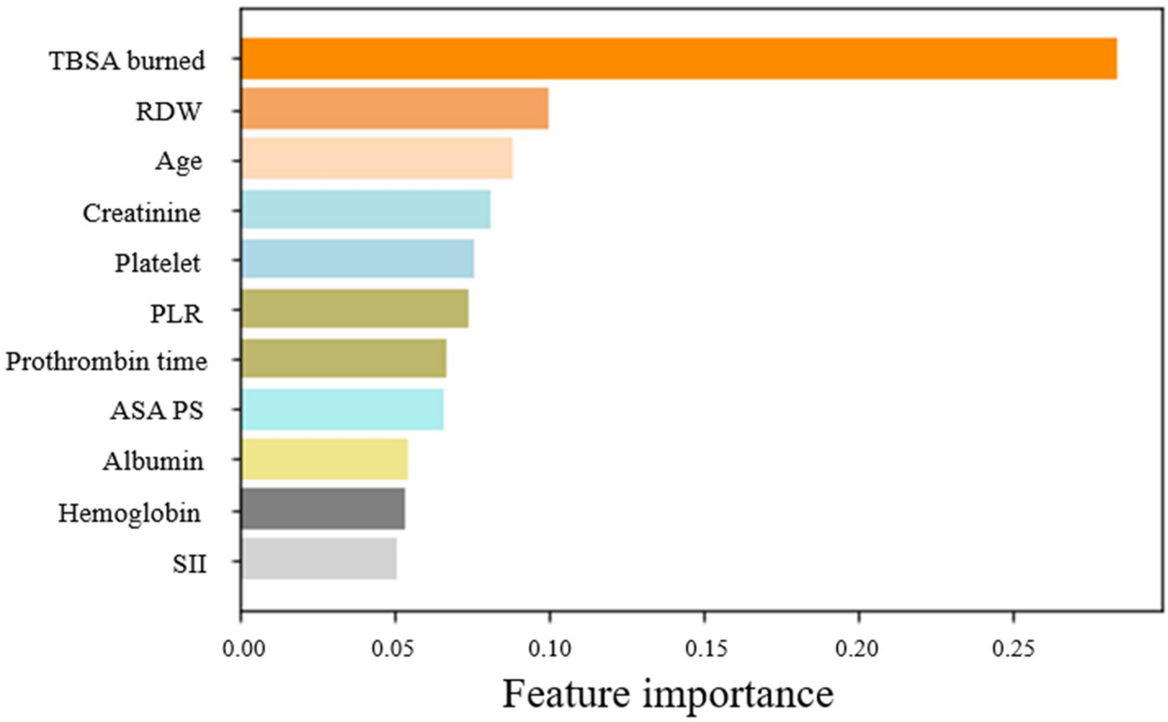
Among 731 patients, survivors were 533 and non-survivors were 198. The mean ages of the training dataset and the test dataset were 53.96 and 58.86, respectively. The basic demographic data of the included patients can be referred to the Table 1.1. As a result of the selection of important features using the random forest regressor, a total of 11 features were selected from the 16 features. The 11 features included were age, ASA, TBSA burned, hemoglobin, RDW, platelet, prothrombin time, albumin, creatinine, PLR, and SII. Of these 11 features, the most significant predictors were TBSA (0.28447 ± 0.28447), RDW (0.10053 ± 0.10053), and age (0.08842 ± 0.08842) (Table 2.1). This is depicted as a histogram in Figure 2.2.

Table 2.1. Each feature importance of the variables associated with mortality after burn surgery.

Variables	Feature importance
TBSA burned	0.28447 ± 0.28447
RDW	0.10053 ± 0.10053
Age	0.08842 ± 0.08842
Creatinine	0.08194 ± 0.08194
Platelet	0.07586 ± 0.07586
PLR	0.07459 ± 0.07459
Prothrombin time	0.06747 ± 0.06747
ASA PS	0.06676 ± 0.06676
Albumin	0.05457 ± 0.05457
Hemoglobin	0.05401 ± 0.05401
SII	0.05139 ± 0.05139

TBSA, total body surface area; RDW, red cell distribution width; ASA PS, American Society of Anesthesiologists physical status; PLR, platelet to lymphocyte ratio; and SII, systematic immune-inflammation index.

Figure 2.2. The plot of feature importance using random forest regressor. This figure shows the importance of each covariates in the final model. TBSA burned, RDW, and age showed the highest feature importance in the machine learning models. TBSA, total body surface area; RDW, red cell distribution width; ASA PS, American Society of Anesthesiologists physical status; PLR, platelet to lymphocyte ratio; and SII, systematic immune-inflammation index.



Diagnostic performance of each machine learning models

Figure 2.3 shows the comparison of AUC among the different machine learning models. Random forest showed the highest AUC (0.922 ± 0.020, 95% CI 0.902-0.942) among the other models with sensitivity and specificity of 66.2% and 93.8%. The AUC of AB, DT, SVM, and LGR were 0.915 ± 0.032 (95% CI 0.883-0.947), 0.769 ± 0.063 (95% CI 0.705-0.833), 0.706 ± 0.123 (95% CI, 0.582-0.829), and 0.917 ± 0.021 (95% CI 0.895-0.939), respectively. Table 2.2 shows AUC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each machine learning models.

Figure 2.3. ROC curve analysis was used to compare the AUC among the different machine learning models and logistic regression model. Random forest model showed the highest AUC (0.922) among the other models. ROC, receiver operating characteristic; RF, random forest; AB, adaptive boosting; DT, decision tree; SVM, support vector machine; and LGR, logistic regression.

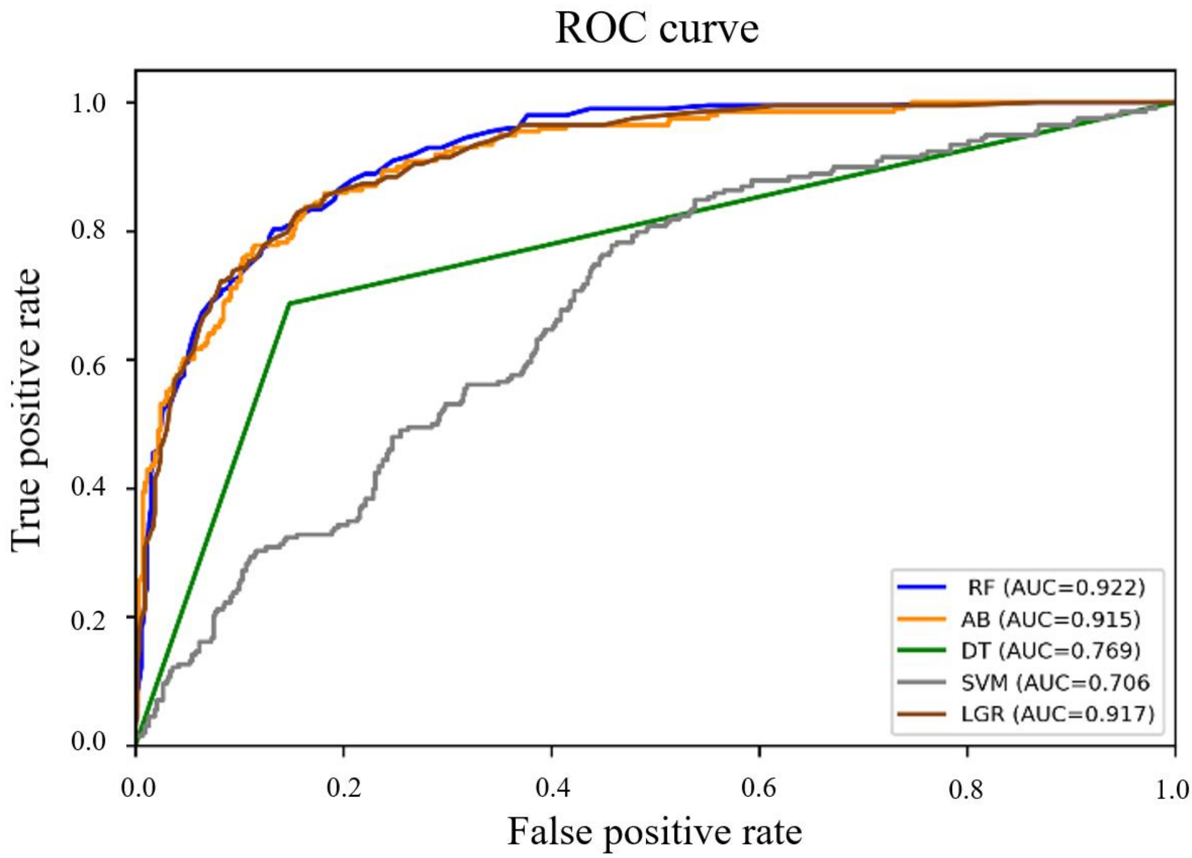


Table 2.2. AUC, sensitivity, specificity, PPV, NPV of each machine learning models

Model	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
RF	0.922 (0.902-0.942)	66.2%	93.8%	79.9%	88.2%
AB	0.915 (0.883-0.947)	69.2%	91.2%	74.5%	88.8%
DT	0.769 (0.705-0.833)	68.7%	85.2%	63.3%	88.0%
SVM	0.706 (0.582-0.829)	3.0%	99.0%	54.5%	73.3%
LGR	0.917 (0.895-0.939)	68.7%	92.7%	77.7%	88.8%

RF, random forest; AB, adaptive boosting; DT, decision tree; SVM, support vector machine; LGR, logistic regression; AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; and NPV, negative predictive value.

Pairwise comparison of AUC among machine learning models

The pairwise comparisons of the AUC using DeLong's test demonstrated that random forest (AUC = 0.922) showed no statistical difference with adaptive boosting (AUC = 0.915) ($p=0.359$) (Table 2.3). However, comparisons with random forest and decision tree (AUC = 0.769), support vector machine (AUC = 0.706), or logistic regression (AUC = 0.917) showed significant difference ($p < 0.05$).

Table 2.3. Pairwise comparisons of area under the receiver operating characteristic curve using DeLong's test.

Model	AUC	95% CI	p-value
RF	0.922 ± 0.020	0.902-0.942	0.359
AB	0.915 ± 0.032	0.883-0.947	
RF	0.922 ± 0.020	0.902-0.942	<0.001
DT	0.769 ± 0.063	0.705-0.833	
RF	0.922 ± 0.020	0.902-0.942	<0.001
SVM	0.706 ± 0.123	0.582-0.829	
RF	0.922 ± 0.020	0.902-0.942	0.042
LGR	0.917 ± 0.021	0.895-0.939	

RF, random forest; AB, adaptive boosting; DT, decision tree; SVM, support vector machine; LGR, logistic regression; AUC, area under the receiver operating characteristic curve; and CI, confidence interval.

2.4 DISCUSSION

In this study, we applied a machine learning approach to clinical features to compare the mortality prediction model in patients after burn surgery. The comparison of AUC among the different machine learning models revealed that RF showed the highest AUC (0.922) among the other models. Also, the pairwise comparisons of the AUC demonstrated that RF showed no statistical difference with AB. However, comparisons with RF and DT, SVM, or LGR showed significant difference.

The present study demonstrated that the top significant predictors for mortality after burn surgery using machine learning were TBSA burned, RDW, and age. Among the clinical features that we have analyzed, TBSA burned constitutes almost 30% of the feature importance among a total of 11 clinical features. Other clinical features of importance by order were RDW, age, creatinine, platelet, PLR, prothrombin time, ASA PS, albumin, hemoglobin, and SII with each less than 10%. TBSA is well known for its strong association with mortality in burn patients.[89,90] Also, RDW showed one of high feature importance among the clinical features. This is a significant finding since age is a well-known major risk factor of mortality in burn patients. Clinical laboratory results such as creatinine, platelet count, prothrombin time, and PLR are significant risk factors in burn patients. This result is consistent with previous studies using classic logistic regression analysis.[11,55] In this study initial 16 clinical features are analyzed with random forest regressor for the selection of 11 important features. Generally, the success of a machine learning algorithm depends on the feature selection and performance criteria for validation.[80] Although many quantitative features can be extracted from medical datasets, these may be highly correlated with each other or simply considered as noise. Thus, it is important to reduce features to select a subset of specific features, enhance the performance, and minimize the computational cost.

Among the machine learning models, our study demonstrated that RF model showed the highest performance that can predict mortality in patients after burn surgery. Also, RF model was not significantly different from AB model. Despite the high AUC values in RF and AB, PPV and NPV were not accordingly high. Thus, it depends on the users of the machine learning models for the selection of which model to use in appropriate clinical situations.

Machine learning approaches are recently reported to have better predictive ability compared to the classic statistical analysis. In the model for predicting AKI, the performance of gradient boosting machine was superior to DT and RF.[91] For machine learning techniques in burn research, burn injury and management can be recognized as patterns that can capture nonlinearities that is shown in independent features such as TBSA burned, age, or inhalation injury which is different from the conventional statistical approaches.[92] Another study about predicting mortality of burn patients was conducted using artificial neural network which included 15 clinical features including inhalation injury, TBSA burned, and admission period.[93] To my knowledge, this study is the first attempt to evaluate the clinical features of the patients after burn surgery using machine learning technique with AUC as the performance metric.

Some limitations should be mentioned. Firstly, since this is a single center study, the particular system characteristics may have contributed to the survival of the patients. Thus, the results could not be generally applied to general population. Secondly, the models use the baseline preoperative characteristics without the postoperative data. Although the dynamic model with sequential data may be superior, the present model in our study predicts mortality in a specific time point which may be significant. Thirdly, the additional data not included in our clinical features could have improved prediction. Further studies are needed with these additional data with common clinical features for clinical acceptance.

2.5 CONCLUSION

This study demonstrated that the most significant predictors for mortality after burn surgery are TBSA, RDW, and age. Random forest showed the best performance for predicting mortality among other models. Also, the pairwise comparisons demonstrated that RF showed no statistical difference with AB. However, comparisons with RF and DT, SVM, or LGR showed significant difference. Further investigation on larger cohort may help support the validity of the machine learning models.

GENERAL CONCLUSION

In this doctoral thesis, the author evaluated prediction ability of preoperative RDW as a prognostic factor of mortality in patients after burn surgery.

The results demonstrate that preoperative RDW could have the ability to predict 90-day mortality in patients after burn surgery. The present study reveals that age, DM, ASA PS III & IV, TBSA burned, RDW, prothrombin time, and creatinine were independent risk factors for mortality in patients after burn surgery. Especially, the novel finding of the present study is that preoperative RDW was considered significant predictor of mortality in patients after burn surgery. Interestingly, as with the survival analysis based on the subgroups of AKI and RDW, patients with AKI and RDW > 12.9 had the lowest survival rate on day 90. Also, the 90-day mortality was 1.24-fold higher in high RDW group than low RDW group. Furthermore, in patients with high RDW prior to burn surgery, postoperative AKI increases the mortality rate further. Therefore, patients with high RDW before burn surgery should be aware of the development of postoperative AKI. Also, machine learning analysis show that the most significant predictors for mortality after burn surgery are TBSA, RDW, and age. The noteworthy finding is that RDW had higher clinical importance compared to age which is considered one of the critical risk factor of mortality in burn patients. Random forest showed the best performance for predicting mortality among other models. Also, the pairwise comparisons demonstrated that RF showed no statistical difference with AB. However, comparisons with RF and DT, SVM, or LGR showed significant difference.

These results suggest that preoperative RDW could be a powerful clinical feature for predicting mortality in patients after burn surgery. The potential risk factors should be considered in the overall management and treatment of the burn patients after the surgery. Further investigation on larger cohort may help support the validity of the machine learning models.

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ABSTRACT IN KOREAN

국문 초록

배경: 화상 손상은 거의 모든 장기 시스템에 영향을 미치고 사망을 초래할 수 있는 치명적인 합병증을 유발할 수 있다. 임상적으로 생존률을 높이기 위해 사망률을 예측하는 것의 중요성을 인정하고 있다. 최근에는 수술 후 사망률을 예측하는 분석 모델을 자동으로 구축하는 진단 성능으로 머신러닝 모델이 주목받고 있다. 환자의 수술 전 변수를 사용하여 사망률을 예측하는 것은 화상 환자에게 최적의 관리를 제공하는 데 도움이 될 수 있다. 이에 저자는 화상 수술 후 환자의 사망률을 예측하는 적혈구 크기 분포 등의 위험인자를 평가하고 임상적 특징도 평가해 머신러닝 기법을 활용한 90일 사망률 예측 모델을 구축했다.

목적: 저자는 고전적 통계 방법과 머신러닝 기법을 사용하여 화상 수술 후 환자의 사망률 예측에 대한 수술 전 위험 요인을 평가하였다.

방법: 진단 검사 소견과 환자의 기본적 특징을 포함한 수술 전 임상적 특징을 수집하였다. 화상 수술 후 사망률에 대한 위험 인자는 단변량 및 다변량 로지스틱 회귀 분석을 사용하여 평가되었다. 또한, 수술 후 급성 신장 손상의 발생률을 평가하였고, 수술 전 적혈구 크기 분포의 수신기 작동 특성 곡선 분석 (area under the receiver operating

characteristic curve analysis, AUC) 을 수행하였다. 90일 사망률은 화상 수술 후 생존율을 비교하기 위해 로그 순위 검정과 함께 Kaplan-Meier 생존 분석을 사용하여 분석하였다. 컷오프 값에 의한 RDW 그룹의 사망률 위험비는 Cox 비례 위험 회귀를 사용하여 분석하였다. 또한, 화상 수술 후 환자의 사망률을 예측하기 위한 임상적으로 중요한 특징을 random forest regressor 를 사용하여 선택하였다. 저자는 random forest, adaptive boosting, decision tree, linear support vector machine, logistic regression 과 같은 머신러닝 알고리즘에 의한 예측의 정확도를 비교하기 위해 수신기 작동 특성 곡선 및 각 모델의 정확도를 분석하였다.

결과: 포함 및 제외 기준을 충족한 환자는 731명이었다. 화상 수술 후 환자의 90일 사망률은 27.1%(198/731)였다. 다변량 로지스틱 회귀 분석 결과 수술 전 변수 중 연령 [Odds ratio, (OR) 1.067; 95% Confidence interval (CI) 1.047-1.088], 당뇨 (OR 3.211; 95% CI 1.288-8.000), 미국마취과학회 신체상태 (American Society of Anesthesiologists physical status, ASA PS) Ⅲ & Ⅳ (OR 4.918; 95% CI 1.581-15.305), 화상총체표면적 (OR 1.095; 95% CI 1.078-1.113), 적혈구 크기 분포 (OR 1.679; 95% CI 1.378-2.046), 프로트롬빈 시간 (OR 4.649; 95% CI 1.259-17.171) 및 크레아티닌 (OR 1.818; 95% CI 1.181-2.798) 은 사망에 대한 독립적인 위험 인자로 간주되었다. 사망률을 분석하기 위해 Cox 비례 위험 회귀를 사용하였으며, 다변수 조정 후의 위험비는 RDW > 12.9 군에서 1.238 (95% CI 1.138-1.347, $p < 0.001$) 이었다. 또한, 수술 후 급성 신장 손상은 생존군보다 비생존군에서 더 발생하였다

(88, 44.4% vs. 30, 5.6%, $p < 0.001$). 머신러닝 모델은 16개의 임상적 특징 중 random forest regressor를 이용하여 총 11개의 임상 특징을 선택하였다. 포함된 11가지 기능은 연령, ASA PS, 화상총체표면적, 헤모글로빈, 적혈구 크기 분포, 혈소판, 프로트롬빈 시간, 알부민, 크레아티닌, 혈소판-림프구 비율 및 전신 면역 감염 지수였다. 이 11가지 임상 특징 중 가장 중요한 예측 변수는 화상총체표면적 (0.28447 ± 0.28447), 적혈구 크기 분포 (0.10053 ± 0.10053) 및 나이 (0.08842 ± 0.08842) 이었다. Random forest는 민감도와 특이도가 각각 66.2%, 93.8%로 다른 모델 중 가장 높은 AUC (0.922 ± 0.020, 95% CI 0.902-0.942)를 보였다. DeLong 테스트를 사용한 AUC의 비교는 random forest 가 (AUC = 0.922)가 adaptive boosting (AUC = 0.915)과 통계적 차이를 보이지 않았다.

결론: 이 연구는 수술 전 적혈구 크기 분포가 화상 수술 후 환자의 90일 사망률을 예측하는 능력이 있음을 보여준다. 또한, 화상 수술 전 적혈구 크기 분포가 높은 환자에서 수술 후 급성 신장 손상은 사망률을 더욱 증가시킨다. 따라서 화상 수술 전 높은 적혈구 크기 분포를 가진 환자는 수술 후 급성 신장 손상의 발달을 인지해야 한다. 또한, 머신러닝 분석을 통하여 화상 수술 후 사망률에 대한 가장 중요한 예측 인자가 화상총체표면적, 적혈구 크기 분포 및 나이라는 것을 입증했다. 여러 모델 중에서 random forest는 다른 모델 중에서 사망률을 예측하는 데 가장 좋은 성능을 보였다.