

DIAGNOSTIC PERFORMANCE OF A MATHEMATICAL FORMULA INTEGRATING SERUM AND BURN BULLA FLUID CREATININE FOR ACUTE KIDNEY INJURY IN SECOND-DEGREE (SUPERFICIAL, MID- AND DEEP-DERMAL) BURNS INVOLVING $\geq 25\%$ TOTAL BODY SURFACE AREA AT DR. SAIFUL ANWAR GENERAL HOSPITAL, EAST JAVA, INDONESIA

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication of extensive burns associated with increased morbidity and mortality. Serum creatinine (SCr) has limited sensitivity for early AKI, and in second-degree burns creatinine may be lost into burn bullae. **Objective:** To evaluate a mathematical formula integrating SCr and burn bulla fluid creatinine (BCr) as a diagnostic parameter for AKI. **Methods:** Observational analytical cross-sectional study of patients with second-degree (superficial, mid- or deep-dermal) burns involving $\geq 25\%$ total body surface area (TBSA) at Dr. Saiful Anwar General Hospital, East Java, Indonesia. SCr and BCr were measured enzymatically and combined, accounting for body weight, body surface area, burn extent and time since injury ($42 \times BW \times SCr + 1.8 \times BCr \times t \times TBSA \times BSA$). AKI was diagnosed by KDIGO 2012 criteria. Performance was assessed by receiver operating characteristic analysis, area under the curve (AUC), cut-off, sensitivity and specificity. **Results:** Thirty patients were included (20 male, 66.7%); AKI occurred in 13 (43.3%). Mean SCr and BCr were 1.18 ± 0.56 and 1.09 ± 0.54 mg/dL. The AUC was 0.910 (95% CI 0.801–1.000; $p < 0.001$). At $\geq 3,305.35$, sensitivity was 84.6%, specificity 82.4%, positive predictive value 78.6% and negative predictive value 87.5%; the highest Youden index occurred at $\geq 3,178.81$ (sensitivity 92.3%, specificity 82.4%). The serum term contributed over 99% of the mean formula value. **Conclusion:** The formula showed excellent discrimination for AKI in extensive second-degree burns, but its performance was driven predominantly by weight-scaled SCr. Correction of the serum-term scaling, assessment of the incremental value of BCr and external validation are required before clinical adoption.

Keywords: Acute Kidney Injury, Burns, Blister Fluid, Creatinine, Diagnostic Accuracy, ROC Curve

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INTRODUCTION

Burn injury remains a major global public health problem. The World Health Organization estimates that burns cause approximately 180,000 deaths every year, the vast majority in low- and middle-income countries. Asia carries a disproportionate share of this burden: an estimated 117 million burns occurred in Asia between 1990 and 2019, and by 2019 the continent accounted for 46% of global burn cases and 47% of burn deaths, with South and Southeast Asia contributing 30–40% of all global cases, deaths and disability-adjusted life years.^{1,2}

In Indonesia, burns accounted for 0.7% of injuries recorded in the 2013 national Basic Health Research survey. Mortality among adult burn patients at the national referral centre in Jakarta has been reported to be high, flame was the predominant mechanism in adults (70.8%) between 2013 and 2015, and a five-year series of 665 patients at Dr. Soetomo General Hospital, Surabaya, reported a case-fatality proportion of 14.1%. Extensive burns therefore continue to carry substantial morbidity and mortality in Indonesian tertiary centres.^{3–6}

Burns are classified by depth, cause and the extent of total body surface area (TBSA) involved, and morbidity and mortality increase with burn size. Burns exceeding 30%

TBSA induce hypovolaemia and release of inflammatory mediators that cause cardiovascular dysfunction, termed burn shock. Increased capillary permeability results in plasma extravasation, increased systemic vascular resistance, reduced peripheral blood flow, reduced cardiac output and diminished urine production, which may progress to acute renal failure, acute tubular necrosis and death if not managed adequately.⁷

Acute kidney injury (AKI) is a common, harmful but potentially reversible decline in renal function if recognised and treated early. According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria, AKI is defined by an increase in serum creatinine (SCr) of ≥ 0.3 mg/dL within 48 hours, an increase to ≥ 1.5 times baseline within the preceding seven days, or a urine output < 0.5 mL/kg/h for six hours. In a Turkish intensive care cohort of burn patients, AKI developed in 54.2%, with a mortality of 34.6% compared with none among those without AKI, and population-based data show that burn-associated AKI is linked to respiratory complications, longer stay, higher costs and mortality during hospitalisation, and to chronic kidney disease, chronic dialysis and long-term mortality one year after injury.^{8–10}

The Emergency Management of Severe Burns course recommends routine laboratory assessment of burn patients that includes urea and creatinine, and at Dr. Saiful Anwar General Hospital SCr is monitored routinely in burn patients.

However, SCr is a limited biomarker of acute injury because it usually rises only 48–72 hours after the insult, which may delay the diagnosis of AKI and reduce the opportunity for early intervention.^{11–13}

In addition, creatinine may be lost extrarenally through burn bulla fluid and wound exudate, potentially lowering SCr and leading to misclassification of AKI. Sosa and colleagues reported creatinine loss through the burn wound and suggested that the open wound acts as an extrarenal site of creatinine loss, and burn wound exudate and blister fluid are known to contain plasma-derived metabolites, including creatinine.^{14–16}

Against this background, the present study evaluated the diagnostic value of a mathematical formula combining SCr and burn bulla fluid creatinine (BCr) for AKI in patients with second-degree (superficial dermal, mid-dermal and deep dermal) burns involving $\geq 25\%$ TBSA at Dr. Saiful Anwar General Hospital, East Java Province, Indonesia.

A. Objectives of the Study

The general objective was to determine whether the mathematical formula of SCr and BCr (the KSL index, from the Indonesian *kreatinin serum dan luka*) can be used as a diagnostic parameter for AKI in patients with second-degree burns involving $\geq 25\%$ TBSA. The specific objectives were (1) to determine the sensitivity and specificity of the formula and (2) to determine its optimal diagnostic cut-off value for AKI.

B. Research Hypothesis

The null hypothesis (H_0) stated that the mathematical formula of SCr and BCr cannot be used as a diagnostic parameter for AKI in patients with second-degree burns at Dr. Saiful Anwar General Hospital, whereas the alternative hypothesis (H_1) stated that it can be used as such a parameter, operationalised as an area under the receiver operating characteristic curve (AUC) greater than 0.5.

C. Significance of the Study

Theoretically, the study contributes to plastic surgery, burn care and nephrology by exploring the use of SCr and BCr as the basis of a mathematical formula for AKI in burn patients and provides a reference for further research on AKI biomarkers and prediction models in burns. Practically, it may provide clinicians with a formula that supports earlier detection of AKI before a meaningful rise in SCr, offer patients earlier evaluation and management that may limit progression of renal injury and complications, and support the development of an AKI screening protocol for burn patients at Dr. Saiful Anwar General Hospital using simple and readily available tests.

LITERATURE REVIEW

A. Definition and Epidemiology of Burns

The American Burn Association defines a burn as damage to the skin and underlying tissues caused by heat, chemicals or electricity. According to the National Burn Repository report covering 2006–2015, burns were more common in men than in women except in those older than 80 years, more than 75%

of reported cases involved less than 10% TBSA, overall mortality was 3.3% and was higher (5.8%) for flame burns, and flame and scald injuries together accounted for 75% of cases. Mortality increased with age, burn size and inhalation injury, and pneumonia was the most frequent complication.^{17,18}

Burns are more common in low- and middle-income countries owing to working conditions, rapid industrialisation, social and cultural factors, political conflict and limited access to surgical care. In Asia, children younger than 5 years bear the greatest burden of disability-adjusted life years, those aged 5–14 years have the highest incidence, and adults older than 70 years have the highest death rate and a mortality ratio of 54%.²

B. Aetiology

Burns result from contact of the skin with thermal, electrical, chemical or radiation energy. Thermal injuries account for about 90% of all burns and include scalds, the most frequent cause and about 70% of burns in children; dry heat injuries from flame or radiant heat, which are common in adults and often accompanied by smoke inhalation; and contact burns, which are typically deep. Electrical injuries account for less than 5% of burns but carry high mortality, chemical burns about 3%, and radiation injuries may cause acute radiation syndrome.⁷

C. Classification of Burns

By depth, burns are classified as epidermal (first degree), partial thickness (second degree) or full thickness (third degree), with deep full-thickness injuries involving muscle, tendon or bone sometimes termed fourth degree (Figure 1). Superficial partial-thickness burns typically form blisters between the epidermis and dermis; because blisters may not form for several hours, a burn initially diagnosed as epidermal may become partial thickness within 12–24 hours. Most superficial partial-thickness burns heal within three weeks without functional impairment or hypertrophic scarring, whereas deep partial-thickness burns extend into the lower dermis, heal in 3–9 weeks with scarring and are usually treated by excision and grafting. Full-thickness burns involve the entire dermis and frequently the subcutaneous fat and heal only by contraction and edge epithelialisation unless grafted.¹⁹

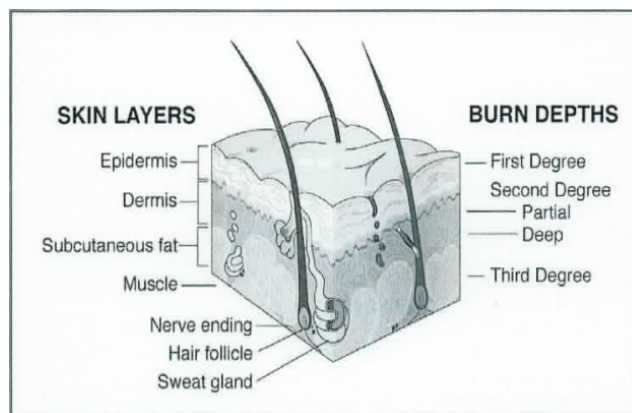


Figure 1: Skin layers and burn depth. Reproduced from Kagan et al.¹⁹

The percentage of TBSA burned in adults is commonly estimated with the Lund–Browder chart (Table 1 and Figure 2) or the Rule of Nines (Figure 3). The Lund–Browder chart is recommended in children because the relative proportions of body regions change with growth. For irregular burns, the palm of the patient's hand with and without the fingers represents approximately 1% and 0.5% of TBSA, respectively, and superficial (first-degree) burns are excluded from the calculation.²⁰

Table 1. Modified Lund–Browder Chart²⁰

Area*	Birth to 1 year	1 to 4 years	5 to 9 years	10 to 14 years	Adult
Head	9.5	8.5	6.5	5.5	4.5
Neck	1	1	1	1	1
Trunk	13	13	13	13	13
Upper arm	2	2	2	2	2
Forearm	1.5	1.5	1.5	1.5	1.5
Hand	1.25	1.25	1.25	1.25	1.25
Thigh	2.75	3.25	4	4.25	4.5
Leg	2.5	2.5	2.5	3	3.25
Foot	1.75	1.75	1.75	1.75	1.75
Buttock	2.5	2.5	2.5	2.5	2.5
Genitalia	1	1	1	1	1

*Values are percentages of total body surface area for one surface (anterior or posterior) of a body region and for one limb.

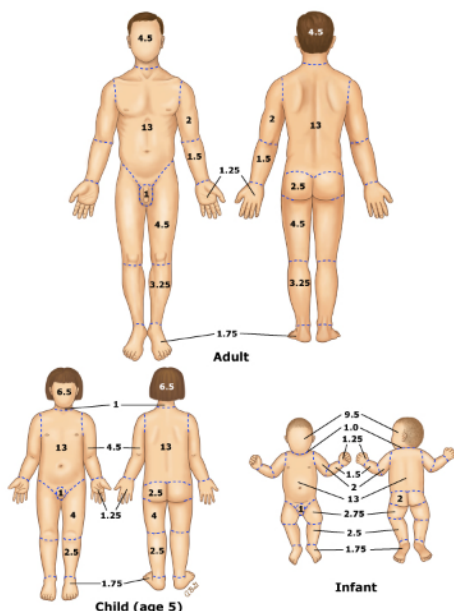


Figure 2: Modified Lund–Browder chart for adults, a 5-year-old child and an infant. Reproduced from Rice and Orgill.²⁰

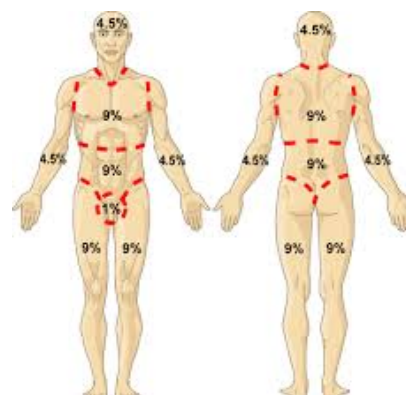


Figure 3: Rule of Nines for estimating burn extent in adults. Reproduced from Rice and Orgill.²⁰

D. Pathophysiology

Locally, burns cause coagulative necrosis of the skin and underlying tissue, and the depth of injury depends on temperature, the energy delivered and the duration of exposure. Three zones are recognised: a zone of coagulation with irreversible necrosis; a surrounding zone of stasis with vascular transudation, vasoconstriction and local inflammation that may recover or progress to necrosis; and an outer zone of hyperaemia with inflammatory vasodilatation that usually recovers unless severe sepsis or prolonged hypoperfusion supervenes.⁷

Systemically, burns exceeding 30% TBSA cause hypovolaemia and release of inflammatory mediators, leading to burn shock, a complex circulatory and microcirculatory disturbance with oedema of burned and unburned tissues. Pulmonary and systemic vascular resistance remain elevated and myocardial depression occurs despite adequate fluid and preload. Oedema formation is biphasic, with a rapid rise in tissue water during the first hour and a slower, progressive phase at 12–24 hours, and a hypermetabolic response driven by catecholamines, cortisol, glucagon, cytokines and reactive oxygen species may double resting energy expenditure in burns exceeding 40% TBSA.⁷

Impaired urine production results from cardiovascular and endocrine disturbances, including altered secretion of angiotensin, vasopressin and aldosterone. Hypovolaemia with reduced cardiac output decreases renal blood flow and glomerular filtration rate (GFR), causing oliguria that, if not managed adequately, may progress to renal failure, acute tubular necrosis and death.⁷

E. Diagnosis

Initial assessment follows trauma principles, with a primary survey of airway with cervical spine protection, breathing and ventilation, circulation with haemorrhage control, disability and exposure, followed by a secondary survey that includes history, pre-injury weight, head-to-toe examination, estimation of TBSA with initiation of fluid resuscitation, laboratory and radiological investigations, monitoring of resuscitation, analgesia, psychosocial support and wound care. Routine screening includes a complete blood count, electrolytes, blood urea nitrogen, glucose and urinalysis, with arterial blood gas and carboxyhaemoglobin when inhalation

injury is suspected. The diagnosis should specify depth, extent, anatomical location and cause, which together determine severity, triage and treatment.^{17,20}

F. Complications and Prognosis

Among 200,867 burn cases reported to the National Burn Repository between 2006 and 2015, the ten most frequent complications were pneumonia, urinary tract infection, cellulitis, respiratory failure, wound infection, septicaemia, renal failure, bacteraemia, arrhythmia and other systemic infections. Although renal failure ranked seventh, AKI carries high mortality, prolongs intensive care stay and increases costs, particularly when renal replacement therapy (RRT) is required.^{9,18}

The revised Baux score combines age, burn size and inhalation injury to predict mortality. In a Saudi burn unit, overall mortality was 17.6%, no patient with a revised Baux score ≥ 110 survived, and inhalation injury and burn size were the most important prognostic factors. AKI after burns is associated with respiratory failure, mechanical ventilation, pneumonia, myocardial infarction, longer stay, higher costs and mortality during the index admission, and with chronic kidney disease, chronic dialysis, readmission and long-term mortality one year after injury.^{10,21,22}

G. Creatinine as a Marker of Renal Function

Creatinine is the breakdown product of creatine and phosphocreatine, which buffer intracellular adenosine triphosphate in muscle; it is produced at a relatively constant rate and excreted predominantly by the kidneys. Because SCr reflects GFR only after a substantial fall in filtration and is influenced by non-renal factors, its rise usually lags 48–72 hours behind the renal insult, limiting its value for early diagnosis of AKI and prompting the search for earlier biomarkers.^{12,13}

H. Burn Bulla Fluid

The World Union of Wound Healing Societies defines wound exudate as material composed of serum, fibrin and white blood cells that escapes into a superficial lesion or area of inflammation. Exudate supports healing by providing a moist environment, allowing diffusion of immune mediators and growth factors, serving as a medium for cell migration, supplying nutrients and supporting autolysis of devitalised tissue.²³

Burn bulla fluid originates from plasma and interstitial fluid after thermal increases in capillary permeability. It contains water, fibrin, glucose, lymphocytes and macrophages, platelets, plasma proteins (albumin, fibrinogen and globulins), growth factors, proteases, metabolic waste products such as urea and creatinine, microorganisms and necrotic debris. The presence of metabolites such as creatinine indicates that bulla fluid reflects interstitial fluid composition and may serve as a source of biomarkers, including for renal dysfunction.^{15,16}

Interstitial fluid is a plasma filtrate with lower protein content, and its volume is maintained by a balance between capillary filtration and lymphatic drainage; according to the revised Starling principle, most interstitial fluid returns to the

circulation via lymphatics. Thermal injury releases histamine, prostaglandins, leukotrienes, bradykinin, tumour necrosis factor- α , interleukin-1 and interleukin-6, which cause vasodilatation, raise capillary hydrostatic pressure, disrupt endothelial junctions and the glycocalyx and damage the extracellular matrix, so that plasma, proteins and inflammatory cells extravasate into the interstitium. When filtration exceeds lymphatic drainage, oedema develops, and in second-degree burns damage to the dermo-epidermal junction allows protein-rich interstitial fluid containing mediators and metabolites such as urea and creatinine to collect between the epidermis and dermis as a bulla.^{16,24,25}

I. Rate and Determinants of Exudate Production

Reported exudate production rates vary with wound type and measurement method (Table 2). Exudate volume is influenced by the cause of the wound, with burns, venous leg ulcers, dehiscent surgical wounds, malignant fungating wounds, inflammatory ulcers and donor sites producing large volumes; by the phase of healing, with production decreasing as healing progresses; by wound size, depth and location, with large, deep and extremity wounds producing more exudate; and by comorbidities and other factors, including infection, surgical debridement, congestive heart failure, renal or hepatic failure, advanced age and drugs such as calcium-channel blockers, non-steroidal anti-inflammatory drugs, corticosteroids and glitazones.^{23,26–28}

Table 2. Exudate Production Rates in Various Wound Types²³

Wound type	Method of measurement	Rate (g/cm ² /24 h)
Leg ulcers	Dressing weight (Dealey et al., 2006)	0.17–0.21
Leg ulcers	Dressing weight (Thomas et al., 1996)	0.43–0.63
Various wounds	Negative pressure wound therapy canister (Dealey et al., 2006)	1.3 mL/cm ² /24 h
Granulating wounds	Vapour pressure gradient, evaporative water loss (Lamke et al., 1977)	0.51
Skin donor sites	Vapour pressure gradient, evaporative water loss (Lamke et al., 1977)	0.42
Partial-thickness burns	Evaporimeter (Ferguson et al., 1991)	0.42–0.86
Partial-thickness burns	Vapour pressure gradient, evaporative water loss (Lamke et al., 1977)	0.43
Full-thickness burns	Vapour pressure gradient, evaporative water loss (Lamke et al., 1977)	0.34

The rate for partial-thickness burns (0.43 g/cm²/24 h) was adopted for the KSL formula. Primary sources: Dealey et al., Lamke et al. and Ferguson et al.^{26–28}

J. Basis of the Mathematical Formula

In extensive second-degree burns, increased microvascular permeability causes large-volume extravasation of plasma into the interstitium and formation of bulla fluid, a plasma ultrafiltrate containing proteins, electrolytes, cytokines, inflammatory mediators, growth factors and metabolites including urea and creatinine. The presence of creatinine in bulla fluid indicates movement of creatinine from the intravascular compartment into wound fluid during the acute phase.¹⁶

Sosa and colleagues reported that burn patients lose creatinine through burn wound exudate, so that the burn wound acts as a site of extrarenal creatinine loss, and that the amount lost is related to the burned surface area and exudate volume. SCr is also limited for early AKI diagnosis because it rises only after a significant fall in GFR and is affected by changes in volume of distribution, haemodilution from resuscitation and loss of creatinine through wound exudate. On this physiological basis, the present study developed a formula integrating SCr and BCr to provide a more representative estimate of total creatinine in the acute phase of burns.¹⁴

K. Previous Studies

Buderer's method, which incorporates the expected sensitivity or specificity, disease prevalence, confidence level and precision, is widely used to determine the sample size of diagnostic accuracy studies. It has been applied in the validation of AKI biomarkers; for example, plasma neutrophil gelatinase-associated lipocalin (NGAL) was validated for diabetes-related AKI with an optimal cut-off of 293 ng/mL, a sensitivity of 80% and a specificity of 87%.^{29,30}

L. Research Gap

Although extrarenal creatinine loss through the burn wound has been described and blister fluid is known to contain creatinine, no study has quantified creatinine in burn bulla fluid and incorporated it into a diagnostic parameter for AKI, and data on early renal assessment in extensive burns from Indonesian tertiary centres remain scarce.^{5,14,16}

M. Novelty

The novelty of this study lies in the use of burn bulla fluid, an easily accessible fluid in second-degree burns, as a source of renal-relevant information, and in combining SCr and BCr into a single formula weighted by body weight, body surface area, burn extent and time since injury, evaluated against KDIGO-defined AKI in adults with burns involving $\geq 25\%$ TBSA using the same routine enzymatic creatinine assay for both fluids.

METHODS

A. Research Design

This was an observational analytical study with a cross-sectional design in patients with second-degree (superficial, mid- and deep-dermal) burns. Serum and bulla fluid samples obtained from patients were analysed in vitro to determine creatinine concentrations, the creatinine measured in bulla fluid was added to that in serum to estimate creatinine content in the absence of extrarenal loss, and the diagnostic value of the result for AKI was then tested statistically.

B. Study Setting

Samples were collected at Dr. Saiful Anwar General Hospital (RSUD Dr. Saiful Anwar), East Java Province, Malang, Indonesia, a provincial tertiary referral and teaching hospital affiliated with the Faculty of Medicine, Universitas Brawijaya. Bulla fluid and serum creatinine were analysed in the Clinical Pathology laboratory of the same institution.

Participants were recruited from the emergency department and the inpatient wards of the Plastic and Reconstructive Surgery subdivision after ethical approval was granted on 2 May 2025.

C. Population and Eligibility Criteria

The target population comprised patients with second-degree (superficial, mid- and deep-dermal) burns, and the accessible population comprised such patients treated at Dr. Saiful Anwar General Hospital. Inclusion criteria were (1) age ≥ 18 years; (2) second-degree burns involving $\geq 25\%$ TBSA; (3) presentation ≤ 48 hours after injury; (4) an intact bulla at the intended aspiration site; and (5) written informed consent.

Exclusion criteria were (1) chronic kidney disease or renal impairment before the burn; (2) ongoing RRT; (3) diseases or conditions known to alter creatinine substantially, such as severe neuromuscular disease or rhabdomyolysis; (4) use of drugs known to affect SCr, such as trimethoprim, cimetidine, dolutegravir or fenofibrate; (5) severe bulla infection or contamination rendering the fluid unsuitable for analysis; and (6) specimens not meeting laboratory requirements, such as severe haemolysis, insufficient volume or contamination. Drop-out criteria were death before completion of the protocol, withdrawal of consent and incomplete data for KDIGO 2012 classification.

D. Sample Size and Sampling

The sample size was estimated with Buderer's formula for diagnostic accuracy studies: $n = Z^2 \times Se \times (1 - Se) / (d^2 \times P)$ for sensitivity and $n = Z^2 \times Sp \times (1 - Sp) / [d^2 \times (1 - P)]$ for specificity, where $Z = 1.96$ for 95% confidence, Se and Sp are the expected sensitivity and specificity (0.80 each), d is the absolute precision (0.20) and P is the prevalence of AKI in burns (0.40). Under these assumptions, the minimum sample is 39 for sensitivity and 26 for specificity. Non-probability saturation sampling was applied, enrolling all eligible patients; the 30 participants analysed met the specificity-based requirement but not the sensitivity-based requirement, so the sensitivity estimate is reported with its 95% confidence interval (CI).²⁹

E. Variables and Operational Definitions

The independent variable was the result of the mathematical formula of SCr and BCr (numerical, ratio scale), and the dependent variable was AKI or no AKI according to KDIGO 2012 (categorical, nominal scale). Operational definitions are presented in Table 3.⁸

Table 3. Operational Definitions of the Study Variables

Variable	Definition and measurement	Scale
1. KSL formula (serum and bulla fluid creatinine)	Sum of the absolute creatinine content of serum and burn bulla fluid, in mg. Bulla fluid sampling: informed consent; selection of the largest, superficially located bulla; antisepsis with 70% alcohol; syringe aspiration; transfer to a serum separator tube (SST); dressing with sterile gauze and bandage. Serum sampling: informed consent; selection of a venipuncture site; proximal tourniquet; 70% alcohol antisepsis; venipuncture with the bevel up; tourniquet release; aspiration; needle withdrawal and dressing; transfer to an SST; monitoring of the puncture site. Laboratory: SST left for 15–30 min; centrifugation at 4,200 rpm for 15 min; analysis on Roche/Hitachi cobas c503; result in mg/dL. Calculation: $KSL = 42 \times BW \times SCr + 1.8 \times BCr \times t \times TBSA \times BSA$.	Numerical (ratio)
2. AKI diagnosis	AKI according to KDIGO 2012. The KSL formula was calculated as in No. 1; urine output was measured at 0, 6, 12, 18, 24, 30, 36, 42 and 48 h and SCr at 48 h. AKI was diagnosed if SCr increased by ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 h, or to ≥ 1.5 times a known or presumed baseline within the prior 7 days, or if urine output was < 0.5 mL/kg/h for 6 h.	Categorical (nominal)

BCr, bulla fluid creatinine (mg/dL); BSA, body surface area (m^2 , Du Bois); BW, body weight (kg); SCr, serum creatinine (mg/dL); t, time since burn injury (h); TBSA, burn extent (fraction of total body surface area).

F. Specimen Processing and Creatinine Assay

Bulla fluid was obtained from intact bullae after aseptic preparation to minimise organic and inorganic contamination, and venous blood was drawn after aseptic preparation. Both specimens were placed in SSTs, left to stand for 15–30 minutes and centrifuged at 4,200 rpm for 15 minutes before analysis. Creatinine was measured quantitatively in vitro on a Roche/Hitachi cobas c503 analyser by an enzymatic method in which creatininase converts creatinine to creatine, creatinase converts creatine to sarcosine and urea, sarcosine oxidase converts sarcosine to glycine, formaldehyde and hydrogen peroxide, and peroxidase catalyses the reaction of hydrogen peroxide with 4-aminophenazone and 2,4,6-triiodo-3-hydroxybenzoic acid to form a quinone imine chromogen whose colour intensity is proportional to the creatinine concentration.

G. Mathematical Formula

The formula estimates total creatinine as the sum of the absolute creatinine content in serum (K_S) and in burn bulla fluid (K_L):

$$K_{S+L} = K_S + K_L = (V_S \times K_S/100) + (V_L \times K_L/100)$$

$$V_S = 0.60 \times V_D; \quad V_D = 70 \text{ mL/kg} \times BW$$

$$V_L = P_L \times (W_L/24) \times L_L \times BSA \times 10,000$$

Here V_S is total serum volume, V_D estimated blood volume, K_S and K_L the creatinine concentrations of serum and bulla fluid (mg/dL), P_L the bulla fluid production rate of partial-thickness burns (0.43 g/cm²/24 h, according to Lamke et al. and Ferguson et al.), W_L the time since burn injury (h), L_L burn extent and BSA the body surface area (m^2) calculated with the Du Bois formula. The computational form applied to all participants was:^{27,28,31}

$$K_{S+L} = 42 \times BW \times K_S + 1.8 \times K_L \times W_L \times L_L \times BSA$$

The bulla-term coefficient follows directly from the derivation ($0.43 \times 10,000/[24 \times 100] \approx 1.8$) and yields milligrams. Dimensional analysis of the serum term, however, gives $0.60 \times 70 \times BW \times K_S/100 = 0.42 \times BW \times K_S$ (mg); the applied constant of 42 therefore scales the serum term 100-fold relative to the absolute serum creatinine mass. Because all reported values, thresholds and ROC estimates derive from the applied form, the index is reported here exactly as computed, in nominal milligram units, and is interpreted as a composite score rather than a physiological creatinine mass (see Limitations).

H. Statistical Analysis

Data were analysed with SPSS version 27. Categorical data are presented as frequencies and percentages. Numerical data were tested for normality with the Shapiro–Wilk test because $n < 50$; normally distributed data are presented as mean and standard deviation (SD), and non-normally distributed data as median with minimum–maximum range.

Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic ability of the formula against KDIGO 2012-defined AKI, plotting sensitivity (true-positive rate) on the Y axis against 1 – specificity (false-positive rate) on the X axis across thresholds. Diagnostic ability was assessed by the AUC with its 95% CI and interpreted as no discrimination (0.5), weak (0.6–0.7), fair (0.7–0.8), good (0.8–0.9) or excellent (> 0.9). The optimal cut-off was defined by the highest Youden index (sensitivity + specificity – 1). Results were then presented in a two-by-two table (Table 4) to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), with Wilson score 95% CIs and likelihood ratios calculated from the cell counts. A p value < 0.05 was considered statistically significant.⁸

Table 4. Two-by-Two Table for Diagnostic Test Analysis

KSL formula	AKI +	AKI –	Total
+	a	b	a + b
–	c	d	c + d
Total	a + c	b + d	N

a, true positive; b, false positive; c, false negative; d, true negative. Sensitivity = $a/(a + c)$; specificity = $d/(b + d)$; positive predictive value = $a/(a + b)$; negative predictive value = $d/(c + d)$.

I. Ethical Considerations

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya (ethical approval No. 161/EC/KEPK-PPDS/05/2025, dated 2 May 2025, valid until 2 May 2026), based on the Declaration of Helsinki. Written informed consent was obtained before sampling, bulla aspiration was performed aseptically on bullae already present as part of the burn, and participant identities were protected by coding.

RESULTS

A. Characteristics of the Participants

Thirty patients were included. Most were male (20; 66.7%), whereas 10 (33.3%) were female (Table 5). Most patients presented 4 hours after injury (16; 53.3%), followed by 2

hours (8; 26.7%), and 3 and 6 hours (3 each; 10.0%) (Table 6). According to KDIGO 2012 criteria, 13 patients (43.3%) developed AKI and 17 (56.7%) did not (Table 7).

Table 5. Characteristics of the Participants by Sex

Sex	Frequency	Percent	Cumulative percent
Male	20	66.7	66.7
Female	10	33.3	100.0
Total	30	100.0	

Table 6. Characteristics of the Participants by Time Since Burn Injury

Time since injury (h)	Frequency	Percent	Cumulative percent
2	8	26.7	26.7
3	3	10.0	36.7
4	16	53.3	90.0
6	3	10.0	100.0
Total	30	100.0	

Table 7. Characteristics of the Participants by AKI Diagnosis

AKI (KDIGO 2012)	Frequency	Percent	Cumulative percent
Yes	13	43.3	43.3
No	17	56.7	100.0
Total	30	100.0	

AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

B. Normality Testing

The Shapiro–Wilk test showed normal distributions for height, body weight, BSA, burn extent, SCr and BCr (all $p > 0.05$), whereas the result of the KSL formula was not normally distributed ($W = 0.911$; $p = 0.016$) (Table 8; Figures 4 and 5). Normally distributed variables are therefore presented as mean $\pm$ SD and the KSL formula as median with range.

Table 8. Normality Tests

Variable	K–S statistic	df	Sig.	S–W statistic	df	Sig.
Height	0.178	30	0.017	0.949	30	0.156
Body weight	0.104	30	0.200*	0.970	30	0.527
BSA	0.094	30	0.200*	0.972	30	0.607
Burn extent	0.121	30	0.200*	0.943	30	0.108
SCr	0.099	30	0.200*	0.950	30	0.166
BCr	0.099	30	0.200*	0.939	30	0.086
KSL formula	0.123	30	0.200*	0.911	30	0.016

*Lower bound of the true significance. K–S, Kolmogorov–Smirnov with Lilliefors significance correction; S–W, Shapiro–Wilk. BCr, bulla fluid creatinine; BSA, body surface area; SCr, serum creatinine.

C. Description of the Study Variables

Mean height was 166.73 ± 5.56 cm (range 155–177), mean body weight 69.10 ± 10.92 kg (51–94) and mean BSA 1.77 ± 0.15 m² (1.48–2.09). Mean burn extent was 0.39 ± 0.10 , equivalent to 38.77% TBSA (25–62%). Mean SCr was 1.18 ± 0.56 mg/dL (0.34–2.88), and mean BCr was 1.09 ± 0.54 mg/dL (0.27–2.81), approximately 92% of mean SCr (Table 9).

Table 9. Descriptive Statistics of Normally Distributed Variables

Variable	N	Minimum	Maximum	Mean	SD
Height (cm)	30	155.00	177.00	166.7333	5.56425
Body weight (kg)	30	51.00	94.00	69.1000	10.91772
BSA (m ²)	30	1.48	2.09	1.7714	0.15399
Burn extent	30	0.25	0.62	0.3877	0.09818
SCr (mg/dL)	30	0.34	2.88	1.1843	0.55812
BCr (mg/dL)	30	0.27	2.81	1.0940	0.54085
Valid N (listwise)	30				

Burn extent is expressed as a fraction of total body surface area. BCr, bulla fluid creatinine; BSA, body surface area; SCr, serum creatinine; SD, standard deviation.

The result of the KSL formula had a median of 3,178.81 nominal mg (range 857.28–10,051.62; interquartile range 2,667.47) and a mean of $3,525.40 \pm 1,973.90$, with positive skewness (1.297) and kurtosis (2.692), indicating wide inter-individual variation (Table 10; Figures 4 and 5). Using cohort means, the bulla term contributed approximately 4.8 nominal mg, or about 0.1% of the mean index value, whereas the serum term contributed more than 99%.

Table 10. Descriptive Statistics of the KSL Formula (Non-Normally Distributed)

Statistic	Value	Std. error
Mean	3525.3991	360.38365
95% CI for mean, lower bound	2788.3318	
95% CI for mean, upper bound	4262.4665	
5% trimmed mean	3376.9401	
Median	3178.8141	
Variance	3896291.211	
Standard deviation	1973.90253	
Minimum	857.28	
Maximum	10051.62	
Range	9194.34	
Interquartile range	2667.47	
Skewness	1.297	0.427
Kurtosis	2.692	0.833

Values in nominal mg. CI, confidence interval.

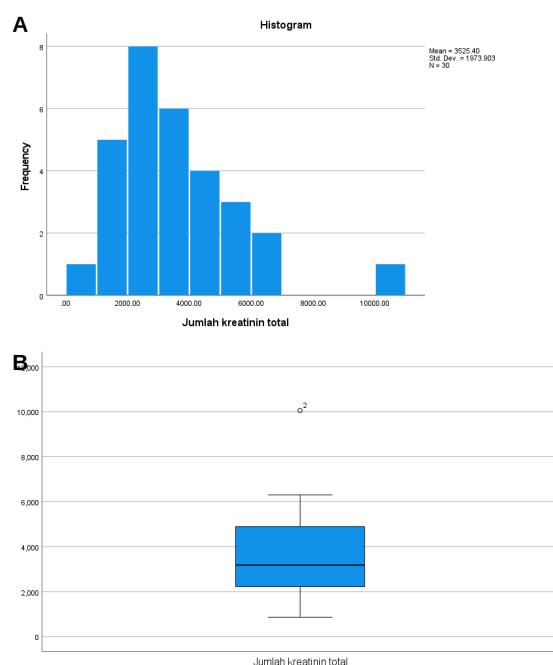


Figure 4: Distribution of the KSL formula ("jumlah kreatinin total") in the 30 participants: (A) histogram with mean 3,525.40 and SD 1,973.90; (B) box plot showing one outlying value.

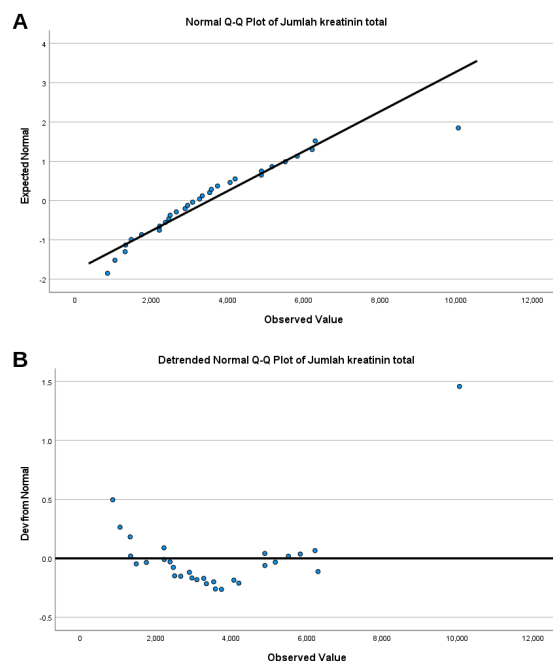


Figure 5: Normality plots of the KSL formula ("jumlah kreatinin total"): (A) normal Q-Q plot; (B) detrended normal Q-Q plot.

D. Receiver Operating Characteristic Analysis

The ROC curve of the KSL formula lay away from the diagonal line and approached the upper-left corner (Figure 6). The AUC was 0.910 (standard error 0.055; asymptotic 95% CI 0.801–1.000; $p < 0.001$), indicating excellent discriminative ability; because the confidence interval did not include 0.5, the null hypothesis was rejected (Table 11).

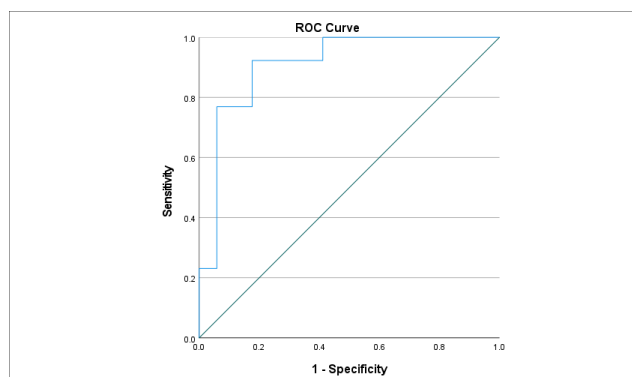


Figure 6: ROC curve of the KSL formula for the diagnosis of AKI (KDIGO 2012). AUC = 0.910 (95% CI 0.801–1.000; $p < 0.001$).

Table 11. Area Under the ROC Curve

Area	Std. error*	Asymptotic sig.†	Lower bound (95% CI)	Upper bound (95% CI)
0.910	0.055	<0.001	0.801	1.000

Test result variable: KSL formula. *Under the non-parametric assumption. †Null hypothesis: true area = 0.5. CI, confidence interval.

The coordinates of the ROC curve are presented in Table 12. The threshold of $\geq 3,305.35$ analysed in the cross-tabulation yielded a sensitivity of 84.6% and a specificity of 82.4%. However, the highest Youden index in the coordinate table (0.747) occurred at the adjacent threshold of $\geq 3,178.81$, which retained the same specificity (82.4%) with a higher sensitivity (92.3%), compared with a Youden index of 0.670 at $\geq 3,305.35$. Sensitivity remained 100% up to a threshold of $\geq 2,481.14$ (specificity 58.8%), and specificity reached 100% from $\geq 6,025.71$ (sensitivity 23.1%).

Table 12. Coordinates of the ROC Curve of the KSL Formula for AKI

Positive if $\geq$	Sensitivity	1 – Specificity
856.2813	1.000	1.000
954.1832	1.000	0.941
1184.7618	1.000	0.882
1324.9892	1.000	0.824
1406.0296	1.000	0.765
1615.1001	1.000	0.706
1982.4771	1.000	0.647
2219.7242	1.000	0.588
2300.3577	1.000	0.529
2420.6003	1.000	0.471
2481.1399	1.000	0.412
2578.5744	0.923	0.412
2774.7431	0.923	0.353
2923.2432	0.923	0.294
3022.2012	0.923	0.235
3178.8141*	0.923	0.176
3305.3523†	0.846	0.176
3437.6525	0.769	0.176
3556.5219	0.769	0.118
3659.8868	0.769	0.059
3905.1056	0.692	0.059
4134.9345	0.615	0.059
4544.7447	0.538	0.059
4890.0840	0.462	0.059
5029.8834	0.385	0.059
5341.5302	0.308	0.059
5672.2721	0.231	0.059
6025.7133	0.231	0.000
6260.9443	0.154	0.000
8175.9572	0.077	0.000
10052.6213	0.000	0.000

*Highest Youden index (0.747). †Threshold analysed in the cross-tabulation (Youden index 0.670). The smallest cut-off value is the minimum observed value minus 1 and the

largest is the maximum observed value plus 1; all other cut-off values are averages of two consecutive ordered observed values.

E. Diagnostic Test Analysis

Cross-tabulation at the threshold of $\geq 3,305.35$ showed 11 patients with AKI and 3 without AKI in the positive group, and 2 patients with AKI and 14 without AKI in the negative group (Table 13). The formula therefore correctly identified 84.6% of patients with AKI (sensitivity; 95% CI 57.8–95.7%) and 82.4% of patients without AKI (specificity; 59.0–93.8%). The PPV was 78.6% (52.4–92.4%) and the NPV 87.5% (64.0–96.5%), with a positive likelihood ratio of 4.79 and a negative likelihood ratio of 0.19.

At the Youden-optimal threshold of $\geq 3,178.81$ derived from Table 12, 12 of 13 patients with AKI and 3 of 17 without AKI would test positive, corresponding to a sensitivity of 92.3% (66.7–98.6%), specificity of 82.4% (59.0–93.8%), PPV of 80.0% (54.8–93.0%), NPV of 93.3% (70.2–98.8%), positive likelihood ratio of 5.23 and negative likelihood ratio of 0.09. The confidence intervals at both thresholds were wide, reflecting the small sample.

Table 13. Cross-Tabulation of the KSL Formula and AKI Diagnosis

KSL formula	Statistic	AKI: yes	AKI: no	Total
$\geq 3,305.35$	Count	11	3	14
	% within KSL category	78.6	21.4	100.0
	% within AKI diagnosis	84.6	17.6	46.7
$< 3,305.35$	Count	2	14	16
	% within KSL category	12.5	87.5	100.0
	% within AKI diagnosis	15.4	82.4	53.3
Total	Count	13	17	30
	% within KSL category	43.3	56.7	100.0
	% within AKI diagnosis	100.0	100.0	100.0

AKI, acute kidney injury (KDIGO 2012).

DISCUSSION

In this study of adults with second-degree burns involving $\geq 25\%$ TBSA, a mathematical formula combining SCr and burn bulla fluid creatinine discriminated patients who developed KDIGO-defined AKI with an AUC of 0.910. Bulla fluid creatinine concentrations were close to serum values, supporting the concept that creatinine enters burn bullae. However, the applied formula was numerically dominated by weight-scaled SCr, so the observed discrimination cannot yet be attributed to the bulla component.

Men outnumbered women (66.7% vs 33.3%), consistent with epidemiological reports showing that burns are more frequent in men, particularly of working age, which probably reflects greater occupational and environmental exposure to heat, fire and electricity. Most patients presented within 4 hours of injury (53.3%), indicating relatively rapid access to care. Early management is critical because the early phase of burns is closely related to burn shock, hypovolaemia, impaired renal perfusion and the risk of AKI.^{6,7,18}

AKI occurred in 43.3% of patients, which is relatively high and in keeping with the 54.2% reported by Kuvvet Yoldaş and colleagues in intensive care burn patients, in whom mean burn extent was 47.3% TBSA among those with AKI. The high incidence reflects the combination of hypovolaemia, burn shock, systemic inflammation, increased vascular permeability, renal hypoperfusion and, later, sepsis. The mean burn extent of 38.8% TBSA in the present cohort is associated with an intense systemic inflammatory response, intravascular fluid loss and a risk of multiorgan dysfunction, and larger burns produce more bulla fluid and potentially greater extrarenal creatinine loss.^{7,9,10}

Mean SCr was 1.18 mg/dL and mean BCr 1.09 mg/dL, indicating that burn bulla fluid contains substantial amounts of creatinine. Creatinine is produced at a relatively constant rate by muscle and excreted mainly by the kidneys; in second-degree burns, damage to the epidermis and dermis increases capillary permeability and generates large volumes of bulla fluid containing plasma components, including small metabolites such as creatinine, which equilibrate between plasma and interstitial fluid.^{16,24,25}

These findings support the observation of Sosa and colleagues that creatinine loss through burn wound fluid may make SCr appear lower than the true creatinine burden, which could delay the diagnosis of AKI if SCr is used as the sole parameter. Widgerow and colleagues similarly described burn wound exudate as containing metabolic products derived from plasma and tissue, so that in extensive burns creatinine loss through bulla fluid may influence the accuracy with which SCr reflects renal function.^{14,15}

ROC analysis is non-parametric and does not require normally distributed data, so it was appropriate despite the non-normal distribution of the formula result. The curve lay away from the diagonal and approached the upper-left corner, and the AUC of 0.910 with a confidence interval excluding 0.5 indicates excellent and statistically significant discrimination between patients with and without AKI. For comparison, plasma NGAL validated for diabetes-related AKI achieved an AUC of 0.85, albeit in a different clinical setting.³⁰

This result must, however, be interpreted in light of the structure of the applied formula. Because the serum term carried a constant of 42, whereas dimensional analysis supports 0.42, the bulla term contributed only about 0.1% of the mean index value, and the index behaved essentially as body-weight-scaled SCr. Had the dimensionally consistent coefficient been applied, the bulla term would have accounted for roughly 12% of the index at cohort means, and diagnostic performance could differ in either direction. The incremental value of bulla fluid creatinine therefore remains untested.

A further consideration is shared-component bias. The SCr measured at enrolment contributed both to the formula and to the creatinine criterion of the KDIGO reference standard, which tends to inflate apparent accuracy. Moreover, the cut-off was derived and evaluated in the same small sample, so the reported sensitivity and specificity are likely optimistic. The highest Youden index in the coordinate table occurred at

$\geq 3,178.81$ rather than at $\geq 3,305.35$; at the latter threshold, sensitivity was lower for the same specificity, so $\geq 3,178.81$ represents the optimal threshold under the stated Youden criterion.⁸

The estimate of bulla fluid volume also rests on strong assumptions. The production rate of $0.43 \text{ g/cm}^2/24 \text{ h}$ was derived from evaporative water loss of open partial-thickness burns measured by vapour pressure gradient, while probe evaporimetry has yielded values up to $0.86 \text{ g/cm}^2/24 \text{ h}$. Intact bullae do not lose fluid by evaporation, exudate volume varies with depth, location, infection and resuscitation, and the short interval from injury to sampling (2–6 hours) further limited the magnitude of the bulla term.^{23,27,28}

Clinically, the formula may become a useful adjunct for early detection of AKI in extensive burns. Current KDIGO-based diagnosis relies on changes in SCr and urine output, and the rise in SCr often appears only 48–72 hours after injury, when delayed diagnosis may increase the risk of multiorgan failure and death. Bulla fluid creatinine can be measured with the same routine enzymatic assay as SCr, making the approach simple and inexpensive. Nevertheless, at its present stage the formula should be regarded as hypothesis-generating and should not replace serial SCr and urine output monitoring.^{8,11,12}

LIMITATIONS AND FUTURE WORK

This study has several limitations. It was conducted in a single centre, so patient characteristics, management patterns and resources may differ from those of other hospitals, and the 30 participants were fewer than the 39 required for the planned precision of sensitivity. Only patients with second-degree burns involving $\geq 25\%$ TBSA and intact bullae were included, so the findings cannot be generalised to other burn depths, smaller burns or patients without bullae. The applied serum-term coefficient (42) is 100-fold larger than that implied by the derivation (0.42), so the formula is a weight-scaled SCr score rather than a physiological creatinine mass. Shared use of enrolment SCr in the index and the reference standard and derivation of the threshold in the same sample may have inflated accuracy. Age, burn aetiology, inhalation injury, resuscitation volumes, AKI stage and the criterion triggering the diagnosis were not reported, bulla fluid volume was estimated rather than measured, and the enzymatic assay has not been formally validated for blister fluid. Finally, the formula was not compared with SCr alone or with newer AKI biomarkers such as NGAL, cystatin C, kidney injury molecule-1 (KIM-1) or tissue inhibitor of metalloproteinases-2 $\times$ insulin-like growth factor-binding protein 7 (TIMP-2-IGFBP7).^{12,30}

Future multicentre studies in more diverse populations should assess the external validity, reproducibility and generalisability of the formula; recompute it with a dimensionally consistent coefficient; compare it with SCr alone and with NGAL, cystatin C, KIM-1 and other novel biomarkers; and refine it by incorporating burn extent, depth, time since injury, resuscitation volume and patient

characteristics, with directly measured bulla fluid volume and pre-specified thresholds.^{12,30}

CONCLUSION AND RECOMMENDATIONS

Conclusion

The mathematical formula of serum and burn bulla fluid creatinine showed excellent diagnostic ability for AKI in patients with second-degree (superficial, mid- and deep-dermal) burns involving $\geq 25\%$ TBSA, with an AUC of 0.910. At the threshold of $\geq 3,305.35$ the formula had a sensitivity of 84.6% and a specificity of 82.4%, whereas the highest Youden index occurred at $\geq 3,178.81$, with a sensitivity of 92.3% and a specificity of 82.4%. Because the applied formula was dominated by weight-scaled SCr, these findings support further investigation but do not yet establish an incremental diagnostic role for bulla fluid creatinine.

Recommendations

1. Clinical: bulla fluid creatinine may be considered as an additional examination in extensive burns within research protocols, the formula may serve as an adjunct parameter in the early phase when SCr has not yet risen, and renal function should be monitored closely from admission in patients with extensive burns.
2. Research: multicentre external validation, evaluation of prognostic value for RRT, length of stay, complications and mortality, comparison with NGAL, cystatin C, KIM-1 and other biomarkers, and refinement of the formula with a dimensionally consistent coefficient and measured bulla fluid volume are required.
3. Hospital: Dr. Saiful Anwar General Hospital may consider developing bulla fluid creatinine testing as part of the laboratory evaluation of extensive burns and should strengthen clinical and laboratory surveillance for AKI in patients with burns involving $\geq 25\%$ TBSA.

DECLARATIONS

Ethics approval: Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya (No. 161/EC/KEPK-PPDS/05/2025; 2 May 2025).

Consent to participate: Written informed consent was obtained from all participants.

Author contributions: KO: conceptualisation, data collection, formal analysis and drafting of the manuscript; HYLW: supervision, methodology, clinical interpretation and critical revision. Both authors approved the final manuscript.

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Conflict of interest: None declared.

Data availability: De-identified data are available from the corresponding author on reasonable request.

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