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Association between lactate to albumin ratio and mortality among sepsis associated acute kidney injury patients

Yaotang Wang[1] and Haixia Yu[2*]

Abstract

Background Sepsis-Associated Acute Kidney Injury (SA-AKI) has high fatality rates, but clear outcome markers are lacking. The objective of this research was to ascertain the link between lactate-to-albumin ratio (LAR) and mortality in cases of SA-AKI.

Methods We performed a retrospective cohort analysis of 3589 critically ill patients with SA-AKI using the Intensive Care Medical Information Mart IV (MIMIC-IV) database. Patients were categorized into four groups based on the quartiles of LAR. The findings of this study provide baseline data and outcomes regarding in-hospital, 30-day, and 90-day mortality rates for SA-AKI patients in the intensive care unit. We utilized multivariate cox regression analysis to compute the adjusted hazard ratio (HR) and 95% confidence intervals (95% CI). Subgroup analysis and restricted cubic spline curves were employed to further investigate the relationship between LAR and mortality.

Results This study involved 3589 participants with a mean age of 62.5 years. Patients in the LAR group with a Q4 (LAR ≥ 0.95) were associated with an increased risk of in-hospital mortality, 30-day mortality, and 90-day mortality (hazards ratio (HR): 2.11, 95% CI:1.7–2.62; HR: 1.9, 95% CI: 1.55–2.34; HR: 1.91, 95% CI: 1.58–2.31, respectively). Notably, within the subgroup of patients with AKI stages 2 and no CHF patients, the association between LAR and mortality was more pronounced.

Conclusion The research underscores that elevated LAR are linked to heightened mortality risks. Notably, subgroup analyses have demonstrated that the correlation between LAR and mortality is particularly robust in certain patient cohorts, most notably those with stage 2 AKI and those without congestive heart failure (CHF).

Clinical trial number Not applicable.

Keywords Septic AKI, Lactate-to-albumin ratio, MIMIC IV

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Introduction

Sepsis is a global health challenge, manifested by an abnormal host response to infection, resulting in organ failure that poses a threat to life [1, 2]. Annually, it impacts millions globally, with the rates of death due to septic shock being approximately one in three, and for sepsis itself, about one in six [3].

SA-AKI, or sepsis-induced acute kidney injury, emerges as a critical issue in global health, imposing a considerable burden of disease. This acute condition, marked by sudden organ malfunction and tissue injury, is suspected to result in chronic negative health impacts. Among patients in intensive care, sepsis is identified as the predominant trigger for AKI, occurring in an estimated 40–50% of cases [4, 5]. The connection between sepsis-induced acute kidney injury (SA-AKI) and poor clinical results is pronounced, with studies showing a markedly increased risk of death for those with sepsis who also experience AKI versus those without such kidney issues. This highlights the necessity for healthcare providers to comprehend and adeptly handle SA-AKI to improve patient outcomes in medical settings [6]. In the context of intensive care, patients experiencing acute kidney injury (AKI) due to sepsis are more likely to face an increased risk of mortality during their hospitalization and tend to have extended lengths of stay in the hospital when compared to those with AKI due to other etiologies [7].

Lactic acid is produced as a result of glycolysis under oxygen-deprived conditions. It is an important indicator of tissue oxygenation, blood perfusion, and metabolism in the body. Under normal physiological conditions, lactate dehydrogenase converts pyruvate into approximately 1500 mmol of lactate daily, with concentrations remaining below 2 mmol/L [8]. In severe conditions characterized by tissue oxygen deprivation and anaerobic metabolism, there is a swift buildup of pyruvate, leading to an increased conversion to lactate [9]. Consequently, elevated lactate levels in the blood, known as hyperlactatemia, frequently occur in patients with critical illnesses. Elevated lactate levels usually imply inadequate tissue perfusion and inadequate oxygenation. Furthermore, the kidney is an important organ of gluconeogenesis, in which lactate is the main substrate of renal gluconeogenesis under physiological conditions. During AKI, altered glycolysis and gluconeogenesis in the kidney can significantly disrupt the lactate metabolic balance, thereby affecting the severity and prognosis of AKI. One study showed that hyperlactatemia, a marker of tissue hypoperfusion and hypoxia, was associated with the development of acute kidney injury (AKI) [10]. In addition, a study of continuous renal replacement therapy (CRRT) in patients with AKI showed that hyperlactatemia was associated with the risk of death [11]. Meanwhile, a retrospective study showed that severe hyperlactatemia, especially without significant lactate clearance, was associated with extremely high ICU mortality [12].

Albumin, a liver-synthesized protein, is closely linked to inflammatory responses in the body. Simultaneously, albumin levels (ALB) serve as a vital gauge of a person's nutritional health and are recognized as a key protein within human plasma. This is due to albumin's role in sustaining the colloidal osmotic pressure of the blood, its involvement in the transportation of various substances throughout the circulatory system, and its facilitation of exchange between intracellular, extracellular, and interstitial fluids [13]. Hypoalbuminemia (HA) is also an indicator of malnutrition or chronic inflammation. Studies have shown that low ALB levels are an independent risk factor for AKI [14]. Meanwhile, a retrospective study showed that low preoperative serum albumin levels were independently associated with AKI and mortality in patients undergoing surgery for brain tumors [15]. In addition, Yu MY et al. study showed that HA is associated with the occurrence of AKI and high mortality in hospitalized patients, and albumin supplementation after AKI may contribute to renal recovery [16].

Considering mechanism description and previous studies, both lactate and albumin levels are associated with adverse outcomes in critically ill patients [11, 14]. And it is noteworthy that biomarkers play an important role in improving disease management in critically ill patients. The lactate/albumin ratio (LAR) has recently received attention as a prospective biomarker and has demonstrated prognostic value in critically ill patients [17, 18]. Shin et al. showed that the area under the curve (AUROC) of the LAR used to evaluate severe sepsis outcome was superior to lactate alone [18]. And recent research has shown the significance of LAR in cases of sepsis and septic shock [19].

Thus, the LAR has the potential to serve as a valuable composite biomarker for assessing the severity and prognosis of patients with SA-AKI. However, the correlation of LAR in SA-AKI patients with its prognosis is still poorly studied. Therefore, this study sought to address this gap by collecting data from the Intensive Care Medical Information (MIMIC)-IV-3.0 database and the primary purpose of this study was to examine the relationship between LAR and outcomes in these patients, thus introducing new insights into the management of patients with SA-AKI.

Materials and methods

Data sources

For a retrospective analysis, we obtained data from the publicly available Intensive Care Medical Information (MIMIC)-IV-3.0 database designed for the medical research community. The team leveraged Structured

Query Language (SQL) with PostgreSQL to extract relevant data from the MIMIC IV database. Access to the MIMIC-IV database was facilitated after the principal investigator completed the required training on the National Institutes of Health platform, including courses on "Study data or Specimens only" and "Conflict of interest" (certification numbers: 59979404 and 59979406).

Study population

The MIMIC-IV database is protected from ethical scrutiny to ensure privacy because of the anonymization patient data, according to MIT's Institutional Review Board. Our study was conducted in accordance with the ethical guidelines of the Helsinki Declaration and in accordance with the Guidelines for the Strengthening of Observational Studies(sTable 1 STROBE checklist) [20].

Out of the total 697,418 admissions recorded in the MIMIC-IV database, 65,366 individuals were identified as having their initial hospital and intensive care unit (ICU) admissions [21, 22]. For participant selection in our study, we included those who fulfilled the subsequent criteria: (1) Patients with sepsis diagnosed according to Sepsis-3; (2) Initial hospitalization and their first-time admission to the Intensive Care Unit (ICU). According to the Sepsis-3 criteria [2], sepsis was identified based on the presence of either a confirmed or suspected infection within the first 24 h following ICU admission, accompanied by a Sequential Organ Failure Assessment (SOFA) score that was equal to or exceeded 2.

After conducting a detailed assessment, the following individuals were excluded from the study: (1) those who did not adhere to the criteria outlined in the Sepsis-3 guidelines; (2)lack of 24-hour blood lactate and serum albumin measurements; (3) Exclusion of patients with missing data on certain physical signs and laboratory tests (including body temperature, systolic blood pressure, oxygen saturation, hematocrit, hemoglobin, anion gap, INR, APTT, ALT, ALP, AST, Bilirubin); and (4) patients were excluded from our study if they did not develop acute kidney injury (AKI) within the first two and seven days following their admission to the intensive care unit (ICU). (5) Patients with a history of kidney disease and those diagnosed with chronic kidney disease are excluded. The workflow is shown in Fig. 1.

Data extraction

We employed Navicat Premium (version 16) to retrieve medical information from the MIMIC-IV database. The clinical data included age, gender, mortality ratio, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiration, oxygen saturation, hematocrit, hemoglobin, anion gap, and international normalized ratio (INR). Comorbidities included myocardial infarction, congestive heart failure, chronic pulmonary disease, malignancy, severe liver disease, and acute kidney injury (AKI) stage. AKI stage 2-day and 7-day referred to the progression staging of AKI after day 2 and day 7 of ICU admission, respectively.

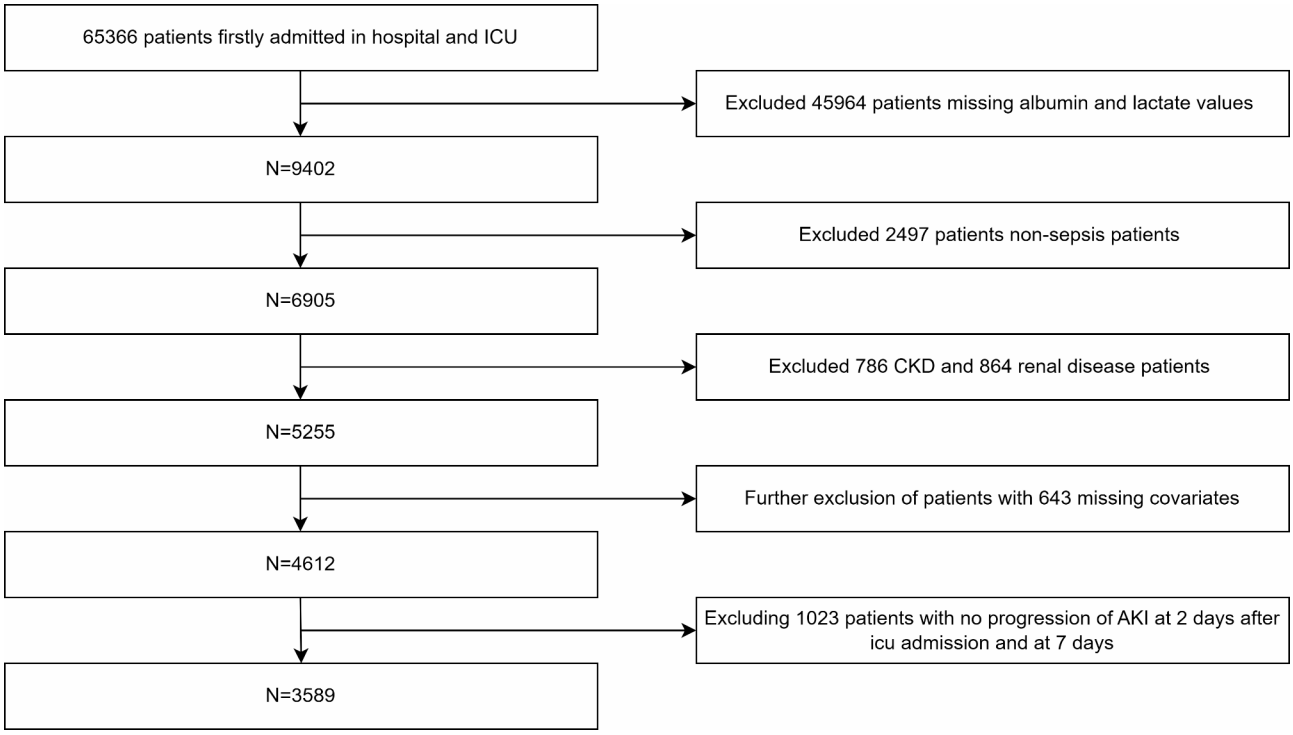

Fig. 1 Flow chart

Treatment measures included the use of anti-infective agents, vasopressors, and Diuretics. Antibiotic drug information included the use of third-generation cephalosporins (Ceftriaxone, Ceftazidime), beta-lactam antibiotics (Ertapenem, Imipenem, Meropenem, Doripenem), fluoroquinolone(Moxifloxacin, Ciprofloxacin), aminoglycoside antibiotics (Gentamicin, Amikacin, Tobramycin). The vasopressors included norepinephrine, dopamine. Diuretics here refer to loop Diuretics. Existing disease conditions were identified using the 9th and 10th Edition Clinical Modification codes.

Exposure

The risk factor LAR was calculated by dividing the lactate level by the albumin level. LAR values were stratified based on their distribution into quartiles. Specifically, LAR was categorized into four groups as per the following quartile ranges: the first quartile was below 0.37; the second quartile spanned from 0.37 to 0.56; the third quartile was between 0.56 and 0.95; and the fourth quartile was 0.95 or higher.

Study endpoints

Within the scope of this research, the primary outcomes measured were mortality rates at in-hospital, 30 days and and 90 days. Furthermore, AKI was determined using both serum creatinine and urine output based on the Kidney disease improving Global Outcomes (KDIGO) criteria [23]. AKI stages were categorized as follows: Stage 1 is characterized by an increase in serum creatinine (Scr) by 1.5 to 1.9 times the baseline value or a 0.3 mg/dl rise in Scr, or a urine output of less than 0.5 ml/kg for 6 to 12 h; Stage 2 is defined by an increase in Scr to 2.0 to 2.9 times the baseline or a urine output of less than 0.5 ml/kg for at least 12 h; Stage 3 is indicated by a Scr level greater than 3 times the baseline or a urine output of less than 0.3 ml/kg for a continuous 24-hour period.

Statistical analysis

In our descriptive analysis, study subjects were stratified into three cohorts according to their LAR quartiles. For continuous variables, we provided the mean ± standard deviation or median with interquartile range (IQR), and we assessed variances between the groups with either ANOVA or Kruskal-Wallis non-parametric test. Categorical variables were expressed as counts or proportions and were scrutinized using the Chi-square test or Fisher's exact test as appropriate.

To evaluate the impact of confounding factors, we incorporated covariates into either a linear regression, or binary logistic regression model as part of the base model, and we sequentially removed these covariates from the comprehensive model and analyzed the resulting changes in the regression coefficients. Covariates that caused a change in the initial regression coefficients by more than 10% were retained in the model. The Variance Inflation Factor (VIF) was employed to assess the presence of multicollinearity. A VIF value exceeding 2 suggests the presence of a collinear relationship. We determined the hazard ratio(HR value) along with their corresponding 95% Confidence Intervals (95%CI) for various LAR levels in relation to clinical outcomes through the application of multivariable Cox proportional hazards regression(Days in ICU were taken as the unit of time). In the initial Model 1, no covariates were adjusted for. Model 2 was adjusted for age, gender, SBP, DBP, MBP, Heart Rate, RR, Temperature, SpO_2, APACHE III score, SOFA score, NE, Dopamine, fluoroquinolone, Aminoglycosides, diuretic, Machine ventilation, Chronic pulmonary disease, Diabetes with complications, severe liver disease.

To scrutinize the relationship between continuous LAR values and the risk of mortality following ICU admission, we utilized Restricted Cubic Spline (RCS) regression analysis. These spline models incorporated the identical set of covariates as were used in the multivariable Cox regression model, which served as our second analytical model. Subgroup analyses along with forest plots were conducted to delineate sensitivity analyses and to evaluate the interplay between LAR and mortality in septic AKI patients, stratified by various factors including age, gender, history of myocardial infarction (MI), presence of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes mellitus (Diabetes), and the severity of acute kidney injury (AKI) categorized at 2 and 7 days post-ICU admission.

A p value less than 0.05 was considered statistically significant to indicate statistical significance, and all tests were two-sided. All the analyses were performed with the R Statistical Software(version 4.2.2, http://www.R-project.org, The R Foundation) and a Free Statistical analysis platform (version 1.9.2, Beijing, China) [24].

Results

Baseline characteristics of the study subjects

In this study, we conducted a thorough analysis of the baseline characteristics of 3,589 patients who were categorized based on the quartiles of LAR, with cutoff values of < 0.37, 0.37 to 0.56, 0.56 to 0.95, and > 0.95(Table 1). The average age of the overall patient population was 62.5 ± 16.3 years, with 42.2% being female and 57.8% being male, showing no significant difference in gender distribution across different LAR groups ($p = 0.057$). Regarding vital signs, we observed a significant increasing trend in the lowest heart rate and respiratory rate as the LAR level increased, especially in the group with LAR > 0.95, which had the highest heart rate ($p < 0.001$). Conversely, the lowest systolic blood pressure, diastolic blood pressure,

Table 1 Baseline characteristics among LAR quartiles

Variables	Total ($n=3589$)	LAR quartiles				
		<0.37 ($n=897$)	**≥0.37,and <0.56 ($n=916$)**	**≥0.56,and <0.95 ($n=874$)**	**≥0.95 ($n=902$)**	***p***
LAR, Median (IQR)	0.6 (0.4, 1.0)	0.3 (0.2, 0.3)	0.5 (0.4, 0.5)	0.7 (0.6, 0.8)	1.7 (1.2, 2.6)	<0.001
Admission age, Mean ± SD	62.5 ± 16.3	62.4 ± 16.4	63.5 ± 15.6	62.2 ± 16.6	61.6 ± 16.4	0.084
Gender, n (%)						0.057
Female	1516 (42.2)	373 (41.6)	360 (39.3)	372 (42.6)	411 (45.6)	
Male	2073 (57.8)	524 (58.4)	556 (60.7)	502 (57.4)	491 (54.4)	
Heart rate min, Mean ± SD	74.6 ± 18.0	68.8 ± 15.7	73.2 ± 16.0	76.5 ± 17.6	79.9 ± 20.6	<0.001
Sbp min, Mean ± SD	83.0 ± 17.1	88.6 ± 14.9	85.9 ± 15.2	83.1 ± 16.7	74.2 ± 18.0	<0.001
Dbp min, Mean ± SD	43.5 ± 11.2	45.5 ± 10.5	44.9 ± 10.4	44.2 ± 10.7	39.5 ± 11.9	<0.001
Mbp min, Mean ± SD	54.1 ± 15.4	57.9 ± 13.7	56.1 ± 14.2	54.3 ± 15.3	47.9 ± 16.3	<0.001
Respiratory rate min, Mean ± SD	13.1 ± 4.4	12.5 ± 3.8	12.7 ± 4.4	13.3 ± 4.4	13.9 ± 5.0	<0.001
Temperature min, Mean ± SD	36.1 ± 1.1	36.3 ± 0.8	36.4 ± 0.8	36.2 ± 1.1	35.7 ± 1.4	<0.001
SpO_2 min, Mean ± SD	89.7 ± 10.2	91.5 ± 6.5	91.3 ± 6.6	90.5 ± 9.2	85.6 ± 15.0	<0.001
APACHE III score, Mean ± SD	63.8 ± 27.8	47.2 ± 20.5	56.6 ± 21.8	65.6 ± 25.4	86.1 ± 27.0	<0.001
Sofa score, Mean ± SD	4.3 ± 2.5	3.4 ± 1.8	4.0 ± 2.2	4.5 ± 2.4	5.4 ± 3.0	<0.001
Dopamine, n (%)						<0.001
No	3225 (89.9)	827 (92.2)	846 (92.4)	780 (89.2)	772 (85.6)	
Yes	364 (10.1)	70 (7.8)	70 (7.6)	94 (10.8)	130 (14.4)	
Diuretics, n (%)						<0.001
No	1461 (40.7)	323 (36)	316 (34.5)	352 (40.3)	470 (52.1)	
Yes	2128 (59.3)	574 (64)	600 (65.5)	522 (59.7)	432 (47.9)	
NE, n (%)						<0.001
No	1397 (38.9)	539 (60.1)	407 (44.4)	297 (34)	154 (17.1)	
Yes	2192 (61.1)	358 (39.9)	509 (55.6)	577 (66)	748 (82.9)	
Machine Ventilation, n (%)						0.502
No	2306 (64.3)	565 (63)	606 (66.2)	563 (64.4)	572 (63.4)	
Yes	1283 (35.7)	332 (37)	310 (33.8)	311 (35.6)	330 (36.6)	
Cephalosporin Antibiotics, n (%)						0.05
No	1538 (42.9)	413 (46)	402 (43.9)	362 (41.4)	361 (40)	
Yes	2051 (57.1)	484 (54)	514 (56.1)	512 (58.6)	541 (60)	
Beta-lactam Antibiotics, n (%)						<0.001
No	3060 (85.3)	812 (90.5)	814 (88.9)	724 (82.8)	710 (78.7)	
Yes	529 (14.7)	85 (9.5)	102 (11.1)	150 (17.2)	192 (21.3)	
Aminoglycosides, n (%)						<0.001
No	3367 (93.8)	865 (96.4)	889 (97.1)	815 (93.2)	798 (88.5)	
Yes	222 (6.2)	32 (3.6)	27 (2.9)	59 (6.8)	104 (11.5)	
Fluoroquinolone, n (%)						<0.001
No	3167 (88.2)	823 (91.8)	818 (89.3)	762 (87.2)	764 (84.7)	

Table 1 (continued)

Variables	Total ($n=3589$)	LAR quartiles				p
		< 0.37 ($n=897$)	≥ 0.37,and < 0.56 ($n=916$)	≥ 0.56,and < 0.95 ($n=874$)	≥ 0.95 ($n=902$)	
Yes	422 (11.8)	74 (8.2)	98 (10.7)	112 (12.8)	138 (15.3)	
In-hospital Mortality, n (%)						< 0.001
No	2463 (68.6)	756 (84.3)	731 (79.8)	604 (69.1)	372 (41.2)	
Yes	1126 (31.4)	141 (15.7)	185 (20.2)	270 (30.9)	530 (58.8)	
30 day Mortality, n (%)						< 0.001
No	2374 (66.1)	732 (81.6)	698 (76.2)	578 (66.1)	366 (40.6)	
Yes	1215 (33.9)	165 (18.4)	218 (23.8)	296 (33.9)	536 (59.4)	
90 day Mortality, n (%)						< 0.001
No	2181 (60.8)	694 (77.4)	652 (71.2)	518 (59.3)	317 (35.1)	
Yes	1408 (39.2)	203 (22.6)	264 (28.8)	356 (40.7)	585 (64.9)	
Myocardial Infarction, n (%)						0.057
No	2996 (83.5)	725 (80.8)	762 (83.2)	744 (85.1)	765 (84.8)	
Yes	593 (16.5)	172 (19.2)	154 (16.8)	130 (14.9)	137 (15.2)	
Congestive Heart Failure, n (%)						0.003
No	2713 (75.6)	663 (73.9)	668 (72.9)	661 (75.6)	721 (79.9)	
Yes	876 (24.4)	234 (26.1)	248 (27.1)	213 (24.4)	181 (20.1)	
Chronic pulmonary disease, n (%)						< 0.001
No	2680 (74.7)	628 (70)	662 (72.3)	669 (76.5)	721 (79.9)	
Yes	909 (25.3)	269 (30)	254 (27.7)	205 (23.5)	181 (20.1)	
Diabetes with complications, n (%)						0.554
No	3446 (96.0)	863 (96.2)	877 (95.7)	834 (95.4)	872 (96.7)	
Yes	143 (4.0)	34 (3.8)	39 (4.3)	40 (4.6)	30 (3.3)	
Malignant cancer, n (%)						< 0.001
No	3078 (85.8)	825 (92)	790 (86.2)	727 (83.2)	736 (81.6)	
Yes	511 (14.2)	72 (8)	126 (13.8)	147 (16.8)	166 (18.4)	
Severe liver disease, n (%)						< 0.001
No	3027 (84.3)	846 (94.3)	776 (84.7)	714 (81.7)	691 (76.6)	
Yes	562 (15.7)	51 (5.7)	140 (15.3)	160 (18.3)	211 (23.4)	
AKIstage-2 day, n (%)						< 0.001
1	892 (24.9)	287 (32)	242 (26.4)	192 (22)	171 (19)	
2	1720 (47.9)	475 (53)	484 (52.8)	425 (48.6)	336 (37.3)	
3	977 (27.2)	135 (15.1)	190 (20.7)	257 (29.4)	395 (43.8)	
AKIstage-7 day, n (%)						< 0.001
1	627 (17.5)	206 (23)	153 (16.7)	132 (15.1)	136 (15.1)	
2	1690 (47.1)	496 (55.3)	494 (53.9)	403 (46.1)	297 (32.9)	
3	1272 (35.4)	195 (21.7)	269 (29.4)	339 (38.8)	469 (52)	

and mean arterial pressure decreased with the increase in LAR levels. Additionally, the lowest body temperature and oxygen saturation also decreased with the increase in LAR levels, being the lowest in the group with LAR > 0.95 ($p < 0.001$). In terms of disease severity scores, both APACHE III and SOFA scores increased significantly with the increase in LAR levels, with the highest scores in the group with LAR > 0.95($p < 0.001$). Regarding treatment and comorbidities, patients with higher LAR levels were more likely to receive treatment with vasoactive drugs including norepinephrine and dopamine, as well as more extensive use of loop Diuretics, beta-lactam antibiotics, fluoroquinolone and aminoglycoside antibiotics ($p < 0.001$). Although there was an increase in the proportion of third-generation cephalosporin antibiotics, this increase was not statistically significant. Furthermore, the proportion of other comorbidities, including myocardial infarction, congestive heart failure, chronic pulmonary disease, malignant tumors, and severe liver disease, also increased with the increase in LAR levels ($p < 0.001$). Moreover, population proportions in acute kidney injury stage 3 varied significantly between groups, with the highest proportion in the LAR Q4 group($p < 0.001$).

LAR is a risk factor for in-hospital/30-day/90-day mortality

LAR was identified as an independent correlate of the in-hospital/30-day/90-day mortality in SA-AKI patients (Table 2). In the unadjusted model (Model 1), LAR was associated with in-hospital/30-day/90-day mortality (HR: 1.39, 95% CI: 1.36–1.43, $P < 0.001$; HR: 1.39, 95% CI: 1.35–1.42, $P < 0.001$; HR: 1.36, 95% CI: 1.32–1.39, $P < 0.001$, respectively). This association remained significant (HR: 1.23, 95% CI: 1.18–1.28, $P < 0.001$; HR: 1.22, 95% CI: 1.17–1.26, $P < 0.001$; HR: 1.22, 95% CI: 1.18–1.27, $P < 0.001$, respectively) even after adjusting for potential confounding factors.

In the quartile stratified analysis, compared to the lowest quartile (Quartile1,<0.37), the highest quartile (Quartile 4,≥0.95) was associated with significantly increased mortality (HR: 4.24, 95% CI: 3.52–5.11, $P < 0.001$; HR: 3.71, 95% CI: 3.11–4.42, $P < 0.001$; HR: 3.19, 95% CI: 2.72–3.74, $P < 0.001$, respectively). In Model 2, Q4 was also associated with mortality (HR: 2.11, 95% CI: 1.7–2.62, $P < 0.001$; HR: 1.9, 95% CI: 1.55–2.34, $P < 0.001$; HR: 1.91, 95% CI: 1.58–2.31, $P < 0.001$, respectively).

In Model 1, Q3 was associated with an increased risk of in-hospital death, 30-day death, and 90-day death relative to Q1 (HR: 1.81, 95% CI: 1.48–2.22, $P < 0.001$; HR: 1.7, 95% CI: 1.40–2.05, $P < 0.001$; HR: 1.61, 95% CI: 1.36–1.92, $P < 0.001$, respectively). In Model 2, Q3 was also associated with the risk of in-hospital death, 30-day and 90-day risk of death relative to Q1 (HR: 1.41, 95% CI: 1.14–1.75, $P = 0.002$; HR: 1.37, 95% CI: 1.12–1.68, $P = 0.002$; HR: 1.42, 95% CI: 1.19–1.71, $P < 0.001$, respectively).

Dose–response relationships

We utilized restricted cubic spline (RCS) models and breakpoint analysis to explore the relationship between LAR and in-hospital mortality, 30-day mortality, and 90-day mortality in SA-AKI patients (Fig. 2). Through this

Table 2 Association between LAR and SA-AKI patients mortality

	Variable LAR	Model 1		Model 2	
		HR (95% CI)	P-Value	HR (95% CI)	P-Value
In-hospital mortality	Per 1 unit	1.39 (1.36–1.43)	< 0.001	1.23 (1.18 ~ 1.28)	< 0.001
	Quartile1(< 0.37)	1(Ref)		1(Ref)	
	Quartile2(≥ 0.37, and < 0.56)	1.2 (0.96–1.5)	0.102	1.09 (0.87 ~ 1.36)	0.436
	Quartile3(≥ 0.56,and < 0.95)	1.81 (1.48–2.22)	< 0.001	1.41 (1.14 ~ 1.75)	0.002
	Quartile4(≥ 0.95)	4.24 (3.52–5.11)	< 0.001	2.11 (1.7 ~ 2.62)	< 0.001
	Trend test	1.71 (1.62–1.82)	< 0.001	1.31 (1.23 ~ 1.41)	< 0.001
30-day mortality	Per 1 unit	1.39 (1.35–1.42)	< 0.001	1.22 (1.17–1.26)	< 0.001
	Quartile1(< 0.37)	1(Ref)		1(Ref)	
	Quartile2(≥ 0.37, and < 0.56)	1.21 (0.99–1.48)	0.066	1.13 (0.92 ~ 1.38)	0.261
	Quartile3(≥ 0.56,and < 0.95)	1.7 (1.4–2.05)	< 0.001	1.37 (1.12 ~ 1.68)	0.002
	Quartile4(≥ 0.95)	3.71 (3.11–4.42)	< 0.001	1.9 (1.55 ~ 2.34)	< 0.001
	Trend test	1.61 (1.53–1.7)	< 0.001	1.25 (1.17 ~ 1.34)	< 0.001
90-hospital mortality	Per 1 unit	1.36 (1.32–1.39)	< 0.001	1.22 (1.18–1.27)	< 0.001
	Quartile1(< 0.37)	1(Ref)		1(Ref)	
	Quartile2(≥ 0.37, and < 0.56)	1.19 (0.99–1.42)	0.068	1.13 (0.94 ~ 1.36)	0.193
	Quartile3(≥ 0.56,and < 0.95)	1.61 (1.36–1.92)	< 0.001	1.42 (1.19 ~ 1.71)	< 0.001
	Quartile4(≥ 0.95)	3.19 (2.72–3.74)	< 0.001	1.91 (1.58 ~ 2.31)	< 0.001
	Trend test	1.52 (1.44–1.6)	< 0.001	1.25 (1.18 ~ 1.33)	< 0.001

HR, hazard ratio; CI, confidence interval; Ref, reference. Model 1 is an unadjusted model, and model 2 is adjusted for Age, gender, SBP, DBP, MBP, Heart Rate, RR, Temperature, SpO_2, APACHE III score, SOFA score, NE, Dopamine, Fluoroquinolone, Aminoglycosides, diuretic, Machine ventilation, Chronic pulmonary disease, Diabetes with complications, severe liver disease

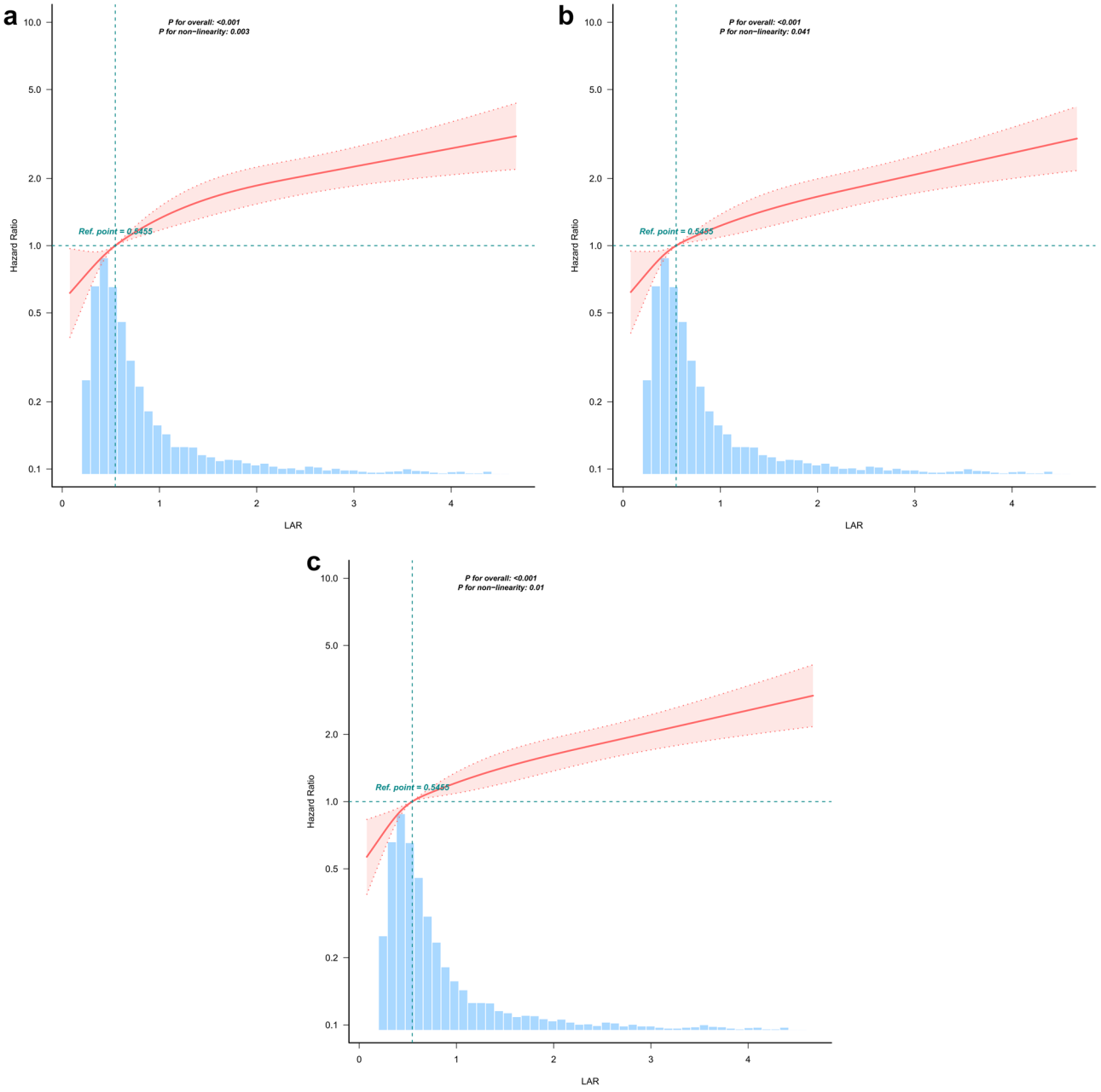

Fig. 2 Non-linear relationship was observed between the Lactate to Albumin Ratio (LAR) and mortality rates during hospitalization, as well as at 30- and 90-days post-admission. The adjustment factors are in accordance with Model 2 from Table 2. In the figure, the red line and shaded red area depict the estimated values and their corresponding 95% confidence intervals, respectively

approach, we aimed to determine the dose-response relationship between LAR and the risk of mortality. Model covariates were adjusted as shown in Table 2, Model 2. The relationships between LAR and in-hospital/30-day/90-day mortality were nonlinear after full adjustment (P for nonlinearity < 0.003, P for nonlinearity = 0.041, P for nonlinearity = 0.01, respectively).

Based on the results of curve fitting, we established the break-point value at 0.55(Table 3). A positive correlation existed between LAR and the risk of in-hospital mortality until reaching a threshold of 0.55 (HR = 2.55, 95% CI: 0.80–8.11, $P = 0.114$). Beyond this threshold, exceeding 0.55, the risk of in-hospital mortality significantly increased (HR = 1.34, 95% CI: 1.23,1.45, $P < 0.001$).

Based on the results of curve fitting, we established the break-point value at 0.55 (Table 3). No significant change existed between LAR and the risk of in-hospital mortality up to a threshold of 0.55 (HR: 2.55, 95% CI: 0.80–8.11, $P = 0.114$). Beyond this threshold, the risk of in-hospital

Table 3 Threshold effect analysis of LAR on in-hospital/30/90/ mortality in SA-AKI patients

Threshold of LAR	In-hospital mortality		30 day-mortality		90 day-mortality	
	HR,95% CI	*P*-value	HR,95% CI	*P*-value	HR,95% CI	*P*-value
< 0.55	2.55 (0.80,8.11)	0.114	2.95 (1.03,8.46)	0.0449	2.93 (1.13,7.65)	0.028
≥ 0.55	1.34 (1.23,1.45)	< 0.001	1.32 (1.22,1.43)	< 0.001	1.32 (1.22,1.42)	< 0.001

The data have been adjusted for all of the factors included in Model 2 in Table 2

HR Hazard ratio, CI confidence interval, LAR lactate to albumin ratio

mortality obviously increased (HR = 1.34, 95% CI: 1.23–1.45, $P < 0.001$).

Similarly, a positive correlation existed between LAR and the risk of 30-day mortality when LAR was below the threshold of 0.55 (HR: 2.95, 95% CI: 1.03–8.46, $P < 0.001$). Once LAR exceeded 0.55, the risk of 30-day mortality also increased (HR: 1.32, 95% CI: 1.22–1.43, $P < 0.001$). A similar threshold effect was observed for 90-day mortality. Below the threshold of 0.55, LAR showed a positive association with the risk (HR: 2.93, 95% CI: 1.13–7.65, $P < 0.001$), and beyond 0.55, the risk escalated (HR: 1.32, 95% CI: 1.22–1.42, $P = 0.028$).

Subgroup analysis and sensitivity analysis

Subgroup analysis examined the relationship between LAR and different mortality endpoints according to age, gender, MI, CHF, COPD, diabetes, and different stages of AKI within 2 and 7 days after ICU admission (sTable 2-4, sFigure 1-3).

When evaluating the relationship between LAR and in-hospital mortality (sTable 2, sFigure 1), we found no significant interaction effects of age and gender (P for interaction = 0.226 and P for interaction = 0.738, respectively). However, the presence or absence of CHF affected HR of LAR (P for interaction = 0.015), with an association between LAR and mortality risk in patients without CHF (HR: 1.19, 95% CI: 1.14–1.24). Additionally, the severity of AKI significantly influenced the statistical power of LAR, particularly among patients with stage 2 AKI (AKI stage 2-day, HR: 1.19, 95% CI: 1.09–1.29 AKI stage 7-day, HR: 1.2, 95% CI: 1.09–1.31).

Regarding the 30-day mortality (sTable 3, sFigure 2), the association between LAR and mortality risk did not significantly differ among different age groups (P for interaction = 0.098), but there was a difference between patients with and without CHF (P for interaction = 0.034), with a statistical power of LAR in patients without a history of CHF (HR: 1.19, 95% CI: 1.14–1.24). The presence or absence of COPD did not significantly affect the statistical power of LAR (P for interaction = 0.45), while the severity of AKI (P for interaction < 0.001) significantly influenced the statistical power of LAR, especially for patients in stage 2 AKI (AKI stage 2-day, HR: 1.2, 95% CI: 1.1–1.3; AKI stage 7-day, HR: 1.22, 95% CI: 1.12–1.33).

In the analysis of 90-day mortality (sTable 4, sFigure 3), the association between LAR and mortality risk significantly differed among different age groups (P for interaction = 0.02), with statistical power of LAR in older patients (HR:1.2, 95% CI:1.14–1.26). The presence or absence of CHF (P for interaction = 0.001) affected the statistical power of LAR, particularly in patients without CHF (HR: 1.19, 95% CI:1.15–1.24). The severity of AKI (P for interaction < 0.001) also significantly influenced the statistical power of LAR, especially in stage 2 AKI patients (AKI stage 2-day, HR: 1.22, 95% CI: 1.13–1.32; AKI stage 7-day, HR: 1.25, 95% CI: 1.15–1.36).

Conclusion

In our retrospective cohort analysis, a correlation was identified between the LAR and mortality rates within the hospital, at 30 days, and at 90 days among SA-AKI individuals. A baseline characteristic found that as the level of LAR increased, vital signs, disease severity scores, significantly deteriorated or increased. Additionally, the proportion of therapeutic interventions and comorbidities significantly rose with increasing LAR levels. Then, our study revealed that the mortality rates for SA-AKI patients were 33.9%, 37.6%, and 39.2% for in-hospital, 30-day, and 90-day periods, respectively, aligning with the known high mortality rates associated with SA-AKI [25].

Besides, LAR is an independent risk factor for mortality in SA-AKI patients, with each unit increase in LAR significantly associated with higher mortality risks within in-hospital, 30-day and 90-day periods, even after adjusting for confounding factors. In the full adjusted model, the risk of in-hospital, 30-day, and 90-day deaths increased by 23%, 22% and 22% for each unit increase in LAR. Then, using RCS models, a nonlinear relationship was found between LAR and mortality in SA-AKI patients. A subgroup analysis revealed that age, CHF and AKI stage 2 were major interaction factors influencing LAR and mortality.

DISCUSSION

This study shows that a high LAR is associated with higher mortality rates. Specifically, a high LAR quartile (≥ 0.95) is a significant risk factor for in-hospital, 30-day, and 90-day mortality in SA-AKI patients. In detail, patients in the highest quartile of LAR (≥ 0.95) had a 2.11-fold increased risk of in-hospital mortality, a 1.90-fold increased risk of 30-day mortality, and a 1.91-fold

increased risk of 90-day mortality compared to those in Quartile 1 (LAR < 0.37). Moreover, the association between LAR and mortality risk did significantly differ across age, CHF and AKI stage subgroups.

Blood lactate has become a recognized indicator for sepsis outcomes, with higher levels correlating with increased risk of mortality from sepsis. Serum lactate has been recognized as a biomarker of sepsis prognosis, and elevated serum lactate levels are positively associated with sepsis mortality [26]. The Sepsis-3 guidelines recommend that persistent serum lactate levels of > 2 mmol/L after adequate fluid resuscitation should be used as the new criterion in the clinical definition of septic shock [2]. Therefore, it is important to normalize lactate in patients with elevated lactate. Various studies have provided considerable evidence on the prognostic value of lactate in critically ill patients [8, 27, 28].

Albumin is an indicator of inflammation and systemic nutritional status, and studies have shown that albumin is associated with prognosis in patients with sepsis [29]. Albumin plays an important role in protecting the kidneys [30–32]. and maintaining renal function by mechanisms that include scavenging reactive oxygen species to prevent oxidative damage [30] and promoting renal perfusion by maintaining concentrations in the interstitium of renal medullary papillae [33]. Lower levels of albumin often indicate a poor prognosis in individuals with AKI [34–36]. Hypoalbuminemia is an important independent factor of death after the development of AKI and AKI. Serum albumin assay can be used to identify patients with an increased risk of death after AKI or AKI [37].

Our results are in line with the growing acknowledgment of lactate and albumin as potential biomarkers for a range of pathological states. Lactate reflects the degree of tissue oxygen deprivation, and albumin plays a role in the antioxidant mechanisms associated with various illnesses Prior studies have demonstrated a substantial correlation between elevated lactate levels and the risk of mortality among patients with suspected infections and sepsis [38]. In a research study focusing on COVID-19 fatalities, similar findings were observed, highlighting an inverse relationship between albumin levels and mortality rates. This suggests that as albumin levels drop, the risk of death increases, which points to the significance of albumin as a prognostic biomarker not only in COVID-19 but also possibly in other medical contexts [39].

Recent research indicates that the LAR holds prognostic value for mortality across a spectrum of conditions, such as heart failure [40], sepsis [41], and acute respiratory distress [42]. A forward-looking study identified that LAR was superior to lactate in evaluating in-hospital mortality in sepsis [43]. Kamran Shadvar et al. [44] conducted a study involving 151 patients with septic shock. They found that LAR was determined to be a more accurate correlate of patient outcomes than lactate levels or lactate clearance. Additionally, a separate study by Cakir et al. [41], including 1136 septic patients admitted to the ICU, LAR was a more dependable biological indicator of clinical outcome in patients with sepsis when compared to the assessment of lactate and albumin respectively.

Consistent with these insights, our study underscores the apparent association between elevated LAR and mortality. Meanwhile, we found some points of concern in the subgroup analysis. We found that for AKI stage 2 as well as for patients without CHF, the HR between LAR and death was more significant, with an interaction between subgroups. AKI stage 2 may easily lead to the accumulation of metabolic waste such as creatinine and urea nitrogen in the body, while the urine volume decreases, further leading to disturbances in water, electrolyte, and acid-base balance. These pathophysiological changes may be more significant in AKI stage 2, therefore the effect of LAR may be higher at this stage. However, the specific mechanisms and theories for why the mortality progression in the AKI stage 2 subgroup is higher than in stages 1 and 3 are not yet fully elaborated. It is speculated that this may be related to the fact that patients in stage 2 of AKI have already experienced a certain degree of tissue hypoxia and metabolic disorder, which requires further basic experimental and theoretical support, as well as in-depth cohort analysis of different population subgroups for confirmation. A retrospective cohort study of 6453 SA-AKI patients highly similar to this study showed that lactate dehydrogenase to serum albumin ratio was associated with poor prognosis in patients with SA-AKI [45]. This highly similar study also analyzed mortality in the AKI subgroup, and their results suggest a more valid association between Lactate dehydrogenase/albumin ratio and mortality in the AKI stage 1 subgroup. Similarly to this analogous study, except that the data cohort and metrics were different, our study analyzed the association of LAR with mortality in the day 2 and 7 AKI stage subgroups at 3 different mortality endpoints to further look at its robustness, and robust results were obtained. So the topic of this debate still needs to be further confirmed in the future. Moreover, for the CHF subgroup, our results reached the completely opposite conclusion of the former. The results of our subgroup analysis indicate that LAR is more potent on mortality outcome in the population without CHF. For the three endpoints, patients with AKI stage 2 at 2-day and 7-day had significantly higher HR values than those with stage 1 and stage 3. In patients without CHF, LAR was associated with a higher mortality risk. For 90-day mortality, patients aged 65 and above had a higher risk compared to other age groups (HR: 1.15, 95% CI: 1.09–1.21).

Limitations

Our research comes with certain limitations that warrant consideration. To begin with, given its nature as a retrospective cohort study conducted at a single center, the applicability of our results to broader populations might be constrained. Additionally, by concentrating on the correlation between the initial LAR post-admission and mortality in SA-AKI patients, our study may not capture the full scope of the relationship between fluctuating LAR values and death rates. Subsequent research endeavors should contemplate incorporating a more dynamic monitoring strategy. Additionally, in the subgroup analysis, we obtained inconsistent results with previous studies, therefore, prospective studies are needed to verify the relationship between LAR and SA-AKI in different subgroups. Despite these shortcomings, our study of the relationship of LAR to the prognosis of SA-AKI individuals remains intriguing.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Yaotang Wang contributed to the planning of the research, the assessment of the findings, and the editing of the paper. Data mining and text editing were performed by Haixia Yu.

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Data availability

The datasets generated and analyzed during the current study are available in the Medical Information Mart for Intensive Care IV (https://physionet.org/content/mimiciv/3.0/).

Declarations

Ethics approval and consent to participate

The study was approved by Massachusetts Institute of Technology Affiliates. (ID: 52390976). The study conformed to the provisions of the Declaration of Helsinki (revised in 2013). The studies involving human participants were reviewed and approved by Institutional Review Board of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

Consent for publication

All authors have approved the manuscript and have provided consent for submission to the journal.

Competing interests

The authors declare no competing interests.

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