eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Comparative Effectiveness of *Channa micropeltes* Albumin Extract Versus Human Albumin on Lactate and Central Venous Oxygen Saturation as Predictors of Mortality in Critically Ill Patients with Hypoalbuminemia: A Double-Blind Randomized Controlled Trial

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ARTICLE INFO

Keywords:
Central venous oxygen saturation
Channa micropeltes
Critical illness
Human albumin
Lactate

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i8.1645

A B S T R A C T

Background: Hypoalbuminemia is highly prevalent in critically ill patients and is linked to impaired tissue perfusion and increased mortality. Human albumin is the gold-standard replacement but is costly and largely imported. *Channa micropeltes* (giant snakehead) albumin extract is a potential economical local alternative, yet comparative evidence on tissue-perfusion biomarkers—lactate and central venous oxygen saturation ($ScvO_2$)—as predictors of mortality is scarce.

Methods: A double-blind randomized controlled trial in the intensive care unit of Dr. Moewardi Regional General Hospital, Surakarta, enrolled 32 adults with serum albumin <2.8 g/dL randomized to oral *Channa micropeltes* extract 5 g every 12 h (n=16) or intravenous 20% human albumin (n=16) for three days. Lactate and $ScvO_2$ were sampled via central venous catheter on day 0 and day 3; mortality was followed to day 4. Analyses included repeated-measures ANOVA, Cohen's d, ROC curves and multivariable logistic regression.

Results: Lactate fell in both arms (*Channa* 5.29±1.32 to 3.52±1.00; human 5.31±0.94 to 3.63±1.09 mmol/L; both $p<0.001$; $d\geq1.5$) and $ScvO_2$ rose (*Channa* +10.53%; human +9.54%; both $p<0.001$), with no between-group difference (Δ lactate $p=0.812$; Δ $ScvO_2$ $p=0.620$). Day-3 biomarker AUCs for mortality were 0.572 and 0.498. Albumin type was not associated with mortality (adjusted OR 0.354; 95% CI 0.067–1.862; $p=0.220$; NNT 16). No serious adverse events occurred.

Conclusion: *Channa micropeltes* albumin extract was non-inferior to human albumin for restoring tissue-perfusion biomarkers, supporting its potential as an economical, locally available alternative in critically ill patients with hypoalbuminemia.

1. Introduction

Albumin is the most abundant circulating plasma protein and a central determinant of physiological homeostasis in critically ill patients, accounting for approximately 70–80% of plasma colloid oncotic pressure while serving as the principal transport vehicle for hormones, fatty acids, cations and drugs. Because hepatic albumin synthesis is suppressed during inflammation, malnutrition and aging, hypoalbuminemia—commonly defined as serum albumin below 3.0 g/dL—is among the most frequent biochemical derangements in the intensive care unit (ICU) and is consistently associated with longer ventilation, infection, organ dysfunction and excess mortality.[1,2,3] In Indonesian tertiary ICUs, where late presentation, sepsis and trauma predominate, severe hypoalbuminemia is particularly common and imposes a substantial therapeutic and economic burden.

Exogenous human albumin remains the reference replacement therapy for severe hypoalbuminemia and is widely used for volume expansion in shock and selected resuscitation scenarios. Beyond its oncotic action it exerts pleiotropic non-oncotic effects relevant to the critically ill—glycocalyx protection, capillary-permeability modulation, antioxidant thiol activity and endotoxin binding—and randomized data confirm that albumin restores arterial pressure and accelerates lactate clearance more rapidly than crystalloid, although a clear survival advantage has been difficult to demonstrate.[4-6] However, human albumin is expensive, depends almost entirely on imported plasma-derived product, and its supply is frequently constrained in low- and middle-income health systems, motivating the search for affordable, locally sourced alternatives.

Channa micropeltes (giant snakehead, locally "*ikan toman*") is a freshwater fish abundant in Indonesian inland waters and traditionally consumed to accelerate wound healing and post-operative recovery. Its flesh contains 6.8–16.7% albumin together with a complete amino-acid profile dominated by lysine and glutamic acid, with the highest protein content (16.8%) in larger fish.[7] A systematic review of snakehead extract reported high albumin content, abundant amino acids, fatty acids and trace minerals, together with down-regulation of nuclear factor-κB and modulation of vascular endothelial growth factor (VEGF), interleukin-6 and matrix metalloproteinase-9, mechanisms that enhance fibroblast proliferation, angiogenesis and immunomodulation during tissue repair.[8] A prior randomized study by our group demonstrated that *Channa micropeltes* albumin raised serum albumin in hypoalbuminemic patients comparably to *Channa striata*, supporting its clinical feasibility.[9]

Contemporary evaluation of albumin therapy should extend beyond static serum albumin to dynamic biomarkers of tissue perfusion that more faithfully reflect oxygen metabolism and prognosis. Serum lactate, the by-product of anaerobic glycolysis, rises during tissue hypoperfusion and impaired cellular oxygen extraction; elevated and slowly clearing lactate is among the most robust predictors of mortality across critical-illness syndromes.[10-12] Central venous oxygen saturation ($ScvO_2$), normally 65–75%, indexes the balance between systemic oxygen delivery and consumption; values below 65% signal inadequate delivery, and abnormal $ScvO_2$ is associated with higher mortality in critically ill cohorts.[13,14] Increasingly, combined or ratio-based use of lactate with albumin or oxygenation indices has been shown to refine mortality prediction and to track microcirculatory injury.[15,16,17]

Despite this rationale, no head-to-head trial has compared *Channa micropeltes* albumin extract with human albumin using lactate and $ScvO_2$ as mortality-predictive endpoints in critically ill patients. Existing studies have focused almost exclusively on serum albumin as the outcome, leaving the comparative effect on sensitive perfusion biomarkers—and on survival—unknown.[9] As a tertiary teaching and referral hospital serving a large catchment in Central Java, Dr. Moewardi Regional General Hospital is well placed to generate such evidence, balancing clinical effectiveness, local availability and cost. We therefore conducted a double-blind randomized controlled trial to test the hypothesis that oral *Channa micropeltes* albumin extract is non-inferior to intravenous human albumin in improving lactate and $ScvO_2$, and to evaluate these biomarkers and treatment type as predictors of short-term ICU mortality.

The clinical and economic stakes of hypoalbuminemia in the Indonesian critical-care system are considerable. Sepsis, major trauma and post-surgical complications—the dominant reasons for ICU admission at national referral hospitals—are each accompanied by an acute-phase fall in albumin synthesis and accelerated transcapillary escape, so that a large proportion of patients are profoundly hypoalbuminemic within the first 48 h of admission. Because serum albumin behaves as a negative acute-phase reactant, its concentration integrates the combined burden of inflammation, capillary leak and malnutrition, and tracks closely with the probability of organ failure and death, a relationship repeatedly confirmed in contemporary ICU cohorts.[1,2,3] Replacement strategies therefore sit at the intersection of physiology, pharmaco-economics and equitable access, and the choice of preparation has direct implications for resource allocation in publicly funded units.

Tissue-perfusion biomarkers occupy a pivotal position in modern resuscitation because they bridge the gap between macro-hemodynamic targets, such as mean arterial pressure, and the ultimate physiological goal of adequate cellular oxygen utilization. Mean arterial pressure may be restored pharmacologically while microcirculatory flow and mitochondrial oxygen

extraction remain deranged—a phenomenon termed loss of hemodynamic coherence. Lactate and $ScvO_2$ are sensitive to precisely this disconnect: persistent hyperlactatemia despite normalized blood pressure signals ongoing anaerobic metabolism, whereas an inappropriately low $ScvO_2$ indicates an unfavorable balance between oxygen delivery and consumption.[10,13,16] Anchoring an albumin-comparison trial to these endpoints therefore tests the interventions where it matters most physiologically, beyond the reductionist surrogate of circulating albumin concentration.

From a translational-medicine perspective, the comparison of a plasma-derived human product with a fish-derived extract is instructive. Human albumin is a single, highly purified molecule whose pharmacology is dominated by oncotic and well-characterized non-oncotic actions, whereas *Channa micropeltes* extract is a complex matrix in which albumin coexists with amino acids, trace elements, fatty acids and bioactive peptides.[7,8] The therapeutic signal generated by the extract may therefore arise from several converging mechanisms—nutritional substrate provision, antioxidant and anti-inflammatory signalling, and modest oncotic support after hepatic re-synthesis of absorbed amino acids—rather than from a single dominant pathway. Framing the trial around perfusion biomarkers rather than serum albumin alone allows these mechanistically distinct interventions to be compared on a common, clinically meaningful endpoint that reflects the adequacy of tissue oxygenation.[10,13]

2. Methods

Study design and setting

This was a prospective, double-blind, parallel-group randomized controlled trial conducted in the Intensive Care Unit (Instalasi Perawatan Intensif) of Dr. Moewardi Regional General Hospital/Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia, between January and March 2026. Reporting follows the CONSORT 2010 statement. The trial was approved by the institutional Health Research Ethics Committee (Approval No. 089/I/HREC/2026) and conducted according to the Declaration of Helsinki; written informed consent was obtained from every participant or legal surrogate.

Participants

Eligible participants were critically ill adults aged 18–65 years admitted to the ICU with serum albumin <2.8 g/dL who had not received albumin replacement within the preceding seven days. Exclusion criteria were known allergy to albumin or fish products, severe hepatic or renal dysfunction, a terminal condition with anticipated survival <24 h, contraindication to enteral feeding, pregnancy or lactation, and concurrent enrolment in another trial. Disease severity at admission was characterized with the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, both validated for ICU mortality prediction and used here for baseline comparability and risk adjustment.[11,15]

Randomization and blinding

Participants were allocated 1:1 by computer-generated permuted-block randomization (variable block size). Allocation was concealed in sequentially numbered, opaque, sealed envelopes opened by an unblinded pharmacist who prepared identical-appearing study products. Treating intensivists, outcome assessors, laboratory personnel and patients remained blinded to allocation throughout the study and analysis.

Intervention protocol

The standardized, reproducible ICU intervention protocol comprised the following numbered steps: (1) ICU admission with continuous electrocardiography, pulse oximetry, invasive or non-invasive arterial pressure and hourly urine-output monitoring; (2) insertion of a central venous catheter via the internal jugular or subclavian vein under ultrasound guidance, with radiographic confirmation of tip position at the cavoatrial junction; (3) baseline (day 0) sampling of central venous blood for lactate and $ScvO_2$ using a calibrated blood-gas analyzer before the first study dose; (4) randomization and blinded administration of the assigned product; (5) in the experimental arm, *Channa micropeltes* albumin extract 5 g administered enterally every 12 h via nasogastric tube for three consecutive days; in the comparator arm, intravenous 20% human albumin infused daily for three days, titrated toward a serum albumin target >2.8 g/dL; (6) protocolized supportive ICU care for both arms, including balanced crystalloid resuscitation, noradrenaline titrated to a mean arterial pressure ≥65 mmHg, lung-protective ventilation and early enteral nutrition;[18,19] (7) repeat day-3 sampling of lactate and

$ScvO_2$ under identical conditions; and (8) follow-up of vital status to day 4.

Outcomes

The pre-specified primary outcomes were the change in serum lactate and in $ScvO_2$ from day 0 to day 3. Secondary outcomes were the discriminative performance (area under the receiver-operating-characteristic curve, AUC) of day-3 lactate and $ScvO_2$ for ICU mortality, the independent association of treatment type with mortality, and treatment safety (serious adverse events, allergic reactions and gastrointestinal intolerance).

Sample size

The sample size was calculated for the comparison of two independent means (two-sided α=0.05, power=80%) assuming a clinically meaningful 20% between-group difference in lactate/$ScvO_2$ consistent with reported biomarker-based prognostic studies, yielding a minimum of 14 participants per arm. Allowing for 10% attrition, 32 participants (16 per arm) were enrolled.[15]

Statistical analysis

Analyses were performed in SPSS 26.0 with two-sided α=0.05. Normality was assessed with the Shapiro–Wilk test. Baseline and biomarker comparisons between arms used the independent-samples t-test or Mann–Whitney U test for continuous data and the chi-square or Fisher's exact test for categorical data. Within-group change from day 0 to day 3 was tested with the paired t-test, and time × group effects with two-way repeated-measures analysis of variance (RM-ANOVA), reporting the F statistic, exact p value and partial eta-squared (η^2p) with Bonferroni adjustment. Standardized effect sizes were expressed as Cohen's d (within-group d from the mean change and averaged standard deviation; between-group d from the pooled standard deviation), interpreted as small (0.2), medium (0.5) and large (0.8). Categorical associations were summarized with the odds ratio (OR) and 95% confidence interval (CI), and the number needed to treat (NNT=1/absolute risk reduction) was derived for the mortality contrast. The prognostic value of day-3 biomarkers for mortality was assessed by ROC analysis (AUC with 95% CI). Independent predictors of mortality were identified by multivariable binary logistic regression; variables with bivariate p<0.25 entered the model and the biomarkers of primary interest were force-entered, with adjusted OR (95% CI) and exact p values reported to three decimal places. Because follow-up was complete for all 32 randomized participants, the intention-to-treat and per-protocol populations were identical and no imputation was required.

Data collection and laboratory measurement

All central venous blood samples were drawn from the distal port of the central venous catheter after discarding the initial dead-space volume, processed immediately and analyzed on a single, daily-calibrated point-of-care blood-gas analyzer to minimize pre-analytical variation. Lactate was reported in mmol/L and $ScvO_2$ as a percentage. APACHE II was computed from the worst values in the first 24 h after admission and SOFA from daily organ-support and laboratory data. Demographic, comorbidity and supportive-therapy variables (vasopressor use, mechanical ventilation, renal replacement) were recorded prospectively on a standardized case-report form to permit adjustment for potential confounders, namely age, sex, SOFA score, primary diagnosis and concurrent supportive therapy.

Definitions and bias control

Critical illness was defined by the need for ICU-level organ support or monitoring at admission. Hypoalbuminemia was operationalized as a measured serum albumin below 2.8 g/dL on the admission biochemistry panel; hyperlactatemia as serum lactate above 2.0 mmol/L and severe hyperlactatemia as above 4.0 mmol/L; and the $ScvO_2$ reference bounds as 65% and 75%. Mortality was defined as all-cause death within the four-day observation window. Selection bias was mitigated by consecutive enrolment and concealed block randomization; performance and detection bias by double blinding and identical-appearing products; and confounding by both randomization and multivariable adjustment. Because all 32 randomized participants contributed complete day-0 and day-3 data, the per-protocol and intention-to-treat populations were identical.

3. Results

Participant flow and baseline characteristics

Thirty-two critically ill patients were enrolled and randomized equally to the *Channa micropeltes* (n=16) and human albumin (n=16) arms; all completed day-3 assessment with no loss to follow-up. As shown in Table

1, the arms were well balanced at baseline, with no significant differences in age (40.50±12.09 vs 43.00±12.29 years; p=0.612; d=0.21), male sex (50.0% vs 43.8%; p=0.649), APACHE II score (19.06±4.48 vs 19.19±3.51; p=0.965; d=0.03), SOFA score (7.44±2.97 vs 5.44±3.20; p=0.088; d=0.65), baseline serum albumin (2.26±0.22 vs 2.34±0.25 g/dL; p=0.296; d=0.34), baseline lactate (5.29±1.32 vs 5.31±0.94 mmol/L; p=0.960; d=0.02) or baseline $ScvO_2$ (57.25±5.09 vs 56.50±3.86%; p=0.633; d=0.17). This baseline homogeneity, detailed in Table 1, confirms successful randomization and permits attribution of post-intervention differences to the assigned therapy.

Table 1. Patient demographics and baseline characteristics.

Variable	C. micropeltes (n=16)	Human albumin (n=16)	p	Effect size
Age, years (mean±SD)	40.50±12.09	43.00±12.29	0.612	d=0.21
Male sex, n (%)	8 (50.0)	7 (43.8)	0.649	φ=0.06
APACHE II score (mean±SD)	19.06±4.48	19.19±3.51	0.965	d=0.03
SOFA score (mean±SD)	7.44±2.97	5.44±3.20	0.088	d=0.65
Serum albumin D0, g/dL	2.26±0.22	2.34±0.25	0.296	d=0.34
Lactate D0, mmol/L	5.29±1.32	5.31±0.94	0.960	d=0.02
$ScvO_2$ D0, %	57.25±5.09	56.50±3.86	0.633	d=0.17

Notes: Independent-samples t-test / chi-square test; p>0.05 indicates baseline homogeneity. SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; D0, day 0; d, Cohen's d; φ, phi coefficient.

Changes in tissue-perfusion biomarkers

Both treatments produced large, highly significant within-group improvements in tissue-perfusion biomarkers from day 0 to day 3, as summarized in Table 2 and illustrated in Figure 1. Serum lactate fell from 5.29±1.32 to 3.52±1.00 mmol/L in the *Channa micropeltes* arm (Δ=−1.77 mmol/L; p<0.001; Cohen's d=1.53) and from 5.31±0.94 to 3.63±1.09 mmol/L in the human albumin arm (Δ=−1.68 mmol/L; p<0.001; d=1.66). RM-ANOVA showed a strong main effect of time for lactate (F(1,30)=53.2; p<0.001; η^2p=0.639) with a non-significant time × group interaction (F(1,30)=0.06; p=0.812; η^2p=0.002), indicating equivalent lactate reduction between arms. As displayed in Figure 1 (Panel B), $ScvO_2$ increased from 57.25±5.09 to 67.78±6.26% (*Channa micropeltes*; Δ=+10.53%; p<0.001; d=1.86) and from 56.50±3.86 to 66.04±5.99% (human albumin; Δ=+9.54%; p<0.001; d=1.94), again with a significant time effect (F(1,30)=61.8; p<0.001; η^2p=0.673) and a non-significant time × group interaction (F(1,30)=0.26; p=0.616; η^2p=0.009). As reported in Table 2, between-group comparison of day-3 values and of the change scores showed no significant difference for either lactate (day-3 p=0.768; Δ p=0.812; between-group d=−0.11) or $ScvO_2$ (day-3 p=0.428; Δ p=0.620; between-group d=0.28), consistent with non-inferiority of the snakehead extract.

Table 2. Tissue-perfusion biomarker changes from day 0 to day 3.

Parameter	C. micropeltes (n=16)	Human albumin (n=16)	Between-group p
Lactate D0, mmol/L	5.29±1.32	5.31±0.94	0.960
Lactate D3, mmol/L	3.52±1.00	3.63±1.09	0.768
Δ Lactate, mmol/L	−1.77	−1.68	0.812
Within-group p (D0→D3)	<0.001	<0.001	—
Within-group Cohen's d	1.53	1.66	—
$ScvO_2$ D0, %	57.25±5.09	56.50±3.86	0.633
$ScvO_2$ D3, %	67.78±6.26	66.04±5.99	0.428
Δ $ScvO_2$, %	+10.53	+9.54	0.620
Within-group p (D0→D3)	<0.001	<0.001	—
Within-group Cohen's d	1.86	1.94	—

Notes: Paired t-test for within-group change; independent-samples t-test for between-group comparison. Two-way RM-ANOVA: lactate time effect F(1,30)=53.2, p<0.001, η^2p=0.639, time × group F(1,30)=0.06, p=0.812; $ScvO_2$ time effect F(1,30)=61.8, p<0.001, η^2p=0.673, time × group F(1,30)=0.26, p=0.616. D0, day 0; D3, day 3; Δ, change.

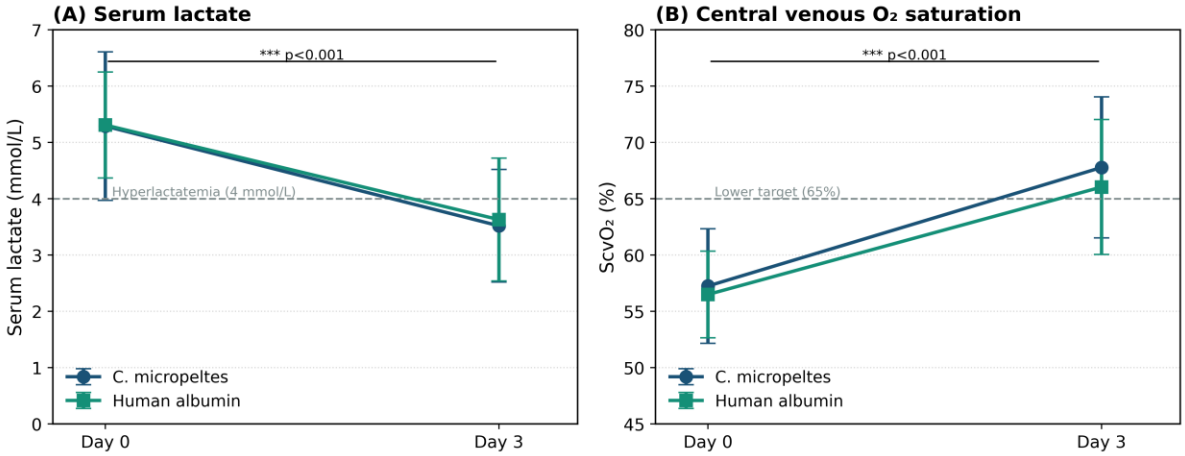

*Figure 1. Trajectories of serum lactate (Panel A) and central venous oxygen saturation ($ScvO_2$, Panel B) from day 0 to day 3 in the two treatment arms. Data are mean±SD; ***p<0.001 for within-group change (paired t-test). Dashed lines mark the 4 mmol/L hyperlactatemia threshold and the 65% lower $ScvO_2$ target.*

Biomarkers and treatment as predictors of mortality

By day 4, 9 patients (28.1%) had survived and 23 (71.9%) had died (*Channa micropeltes* 11/16 deaths, 68.8%; human albumin 12/16 deaths, 75.0%). As detailed in Table 3, day-3 lactate and $ScvO_2$ did not differ significantly between survivors and non-survivors (lactate 3.52±1.55 vs 3.65±0.89 mmol/L, p=0.904; $ScvO_2$ 67.12±6.22 vs 66.83±6.30%, p=0.815). ROC analysis, shown in Figure 2, yielded areas under the curve close to the null for both day-3 lactate (0.572; 95% CI 0.265–0.759) and day-3 $ScvO_2$ (0.498; 95% CI 0.242–0.714), in keeping with the bivariate findings and most plausibly reflecting type II error given the modest sample. The direction of effect—higher lactate and lower $ScvO_2$ among non-survivors—remained physiologically coherent.

Table 3. Day-3 biomarkers by mortality status and ROC performance.

Parameter (D3)	Survivors (n=9)	Non-survivors (n=23)	p	AUC (95% CI)
Lactate, mmol/L	3.52±1.55	3.65±0.89	0.904	0.572 (0.265–0.759)
$ScvO_2$, %	67.12±6.22	66.83±6.30	0.815	0.498 (0.242–0.714)

Notes: Independent-samples t-test / Mann–Whitney U test; ROC, receiver-operating-characteristic curve; AUC, area under the curve; CI, confidence interval. Overall ICU mortality 23/32 (71.9%).

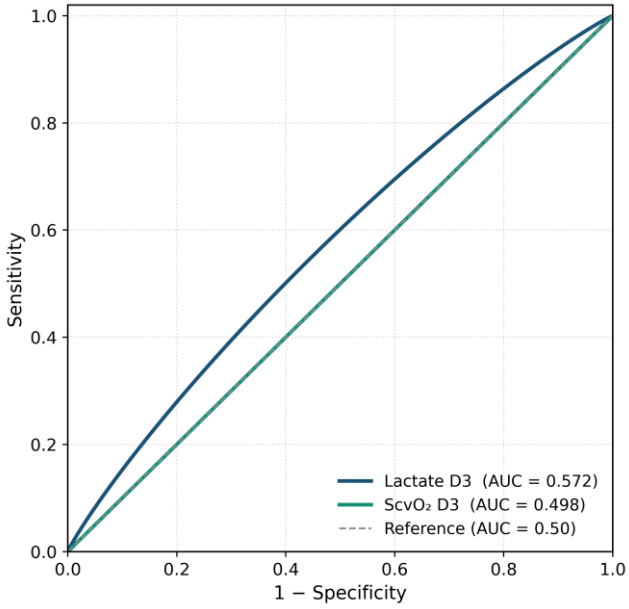

Figure 2. Receiver-operating-characteristic curves of day-3 serum lactate (AUC=0.572) and day-3 $ScvO_2$ (AUC=0.498) for prediction of ICU mortality. Both curves approximate the reference line (AUC=0.50), consistent with limited discrimination in this small cohort.

Multivariable predictors of mortality

In the multivariable logistic-regression model presented in Table 4 and visualized as a forest plot in Figure 3, none of the candidate predictors—treatment group (p=0.220), day-3 lactate (p=0.465), day-3 $ScvO_2$ (p=0.787) or APACHE II score (p=0.883)—was an independent predictor of mortality. Critically, the adjusted OR for treatment group was 0.354 (95% CI 0.067–1.862), indicating that substituting *Channa micropeltes* extract for human albumin did not increase—and numerically tended to lower—the odds of death. As also shown in Table 5, the crude between-arm mortality contrast was non-significant (OR 0.733; 95% CI 0.156–3.450; p=0.694; absolute risk reduction 6.25%; NNT 16), supporting the non-inferiority interpretation.

Table 4. Multivariable logistic-regression predictors of ICU mortality.

Predictor	B	Adjusted OR	95% CI	p
Therapy group (C. micropeltes vs human)	−1.038	0.354	0.067–1.862	0.220
Lactate D3 (per mmol/L)	0.303	1.354	0.599–3.060	0.465
$ScvO_2$ D3 (per %)	−0.018	0.982	0.859–1.122	0.787
APACHE II (per point)	−0.017	0.983	0.787–1.229	0.883

Notes: Binary logistic regression; B, regression coefficient; OR, odds ratio; CI, confidence interval. An OR <1 for therapy group indicates no increased mortality risk with Channa micropeltes extract.

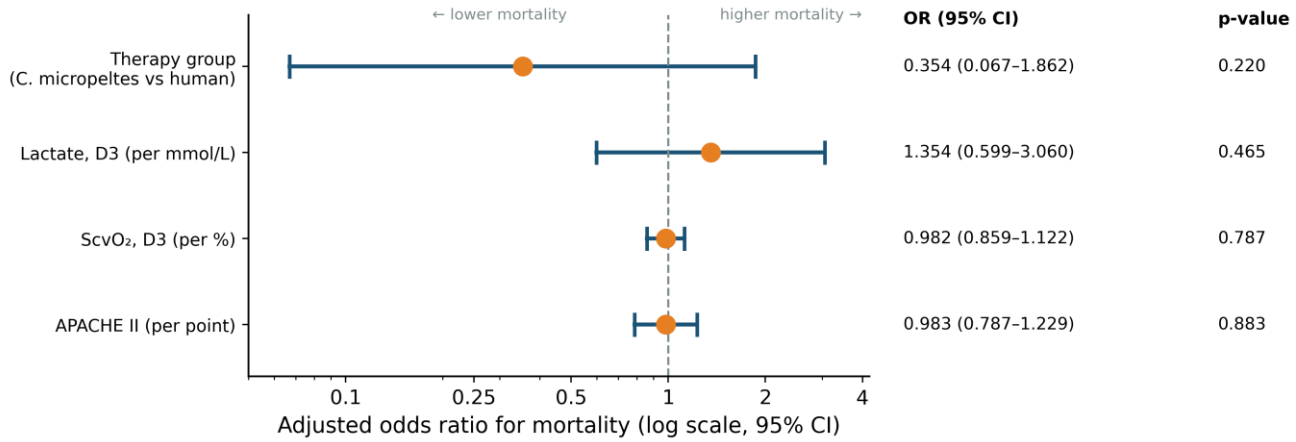

Figure 3. Forest plot of adjusted odds ratios (95% CI) from multivariable logistic regression for ICU mortality. No predictor reached statistical significance; the therapy-group OR of 0.354 indicates no increased mortality risk with Channa micropeltes extract.

Safety and tolerability

As summarized in Table 5, no serious adverse events, anaphylactic reactions or gastrointestinal intolerance requiring discontinuation occurred in either arm during the observation period. All 16 patients assigned to enteral *Channa micropeltes* extract tolerated administration fully (100%), confirming an acceptable safety profile of the oral preparation in a critically ill population.

Table 5. Safety, tolerability and mortality outcomes.

Outcome	C. micropeltes (n=16)	Human albumin (n=16)	OR (95% CI); p
Serious adverse event, n (%)	0 (0.0)	0 (0.0)	—
Allergic/anaphylactic reaction, n (%)	0 (0.0)	0 (0.0)	—
Gastrointestinal intolerance, n (%)	0 (0.0)	0 (0.0)	—
Full enteral tolerance, n (%)	16 (100.0)	NA (intravenous)	—
ICU mortality to day 4, n (%)	11 (68.8)	12 (75.0)	0.733 (0.156–3.450); 0.694

Notes: Fisher's exact test; OR, odds ratio; CI, confidence interval; NA, not applicable. Absolute risk reduction 6.25%; number needed to treat 16.

Internal consistency of the biomarker response

The convergence of three analytic approaches reinforced the principal finding of therapeutic equivalence, as captured across Table 2 and Figure 1. First, paired within-group testing demonstrated large effects in both arms (all $p<0.001$; Cohen's d 1.53–1.94). Second, RM-ANOVA confirmed a dominant main effect of time with a negligible time × group interaction for both lactate ($\eta^2p=0.002$) and $ScvO_2$ ($\eta^2p=0.009$), indicating that the temporal improvement did not depend on the assigned therapy. Third, direct between-group comparison of change scores was non-significant with trivial-to-small effect sizes (lactate between-group d=−0.11; $ScvO_2$ between-group d=0.28), as listed in Table 2. Baseline lactate and $ScvO_2$ were statistically indistinguishable between arms (p=0.960 and p=0.633; Table 1), so the parallel day-3 trajectories shown in Figure 1 cannot be attributed to differential starting points.

4. Discussion

In this double-blind randomized controlled trial of critically ill adults with hypoalbuminemia, oral *Channa micropeltes* albumin extract and intravenous human albumin produced large and statistically indistinguishable improvements in two clinically important tissue-perfusion biomarkers—serum lactate and $ScvO_2$—over three days, with no between-group difference in change scores and no excess mortality attributable to the snakehead preparation. Together with an excellent safety and enteral-tolerance profile, these findings (summarized in Tables 2–5 and Figures 1–3) provide the first head-to-head, biomarker-based evidence that *Channa micropeltes* extract is non-inferior to human albumin for restoring tissue oxygenation in this population.

The balanced baseline severity of the two arms (Table 1)—including near-identical APACHE II scores (19.06 vs 19.19) and comparable SOFA scores—strengthens causal attribution by minimizing confounding from illness severity, an essential prerequisite in critical-care randomized trials.[11,15] The magnitude of lactate reduction ($\Delta \approx -1.7$ mmol/L; Cohen's d ≈ 1.5–1.7) and $ScvO_2$ elevation ($\Delta \approx +10\%$; d ≈ 1.9) is clinically meaningful, moving cohort means from the hyperlactatemic, oxygen-debt range toward recommended resuscitation targets, concordant with evidence linking effective resuscitation and albumin repletion to improved lactate clearance and venous oxygenation.[4,5,10]

For human albumin, the improvement in perfusion biomarkers is readily explained by its classical oncotic mechanism: rapid plasma-volume expansion augments cardiac output and microvascular flow, interrupting anaerobic glycolysis and accelerating lactate clearance, an effect reproducibly observed in randomized trials of goal-directed colloid resuscitation.[4-6] In addition, the non-oncotic properties of albumin—glycocalyx preservation, antioxidant thiol activity and capillary-permeability modulation—contribute to microcirculatory recovery beyond simple volume effects.

For *Channa micropeltes*, an equivalent biomarker response despite enteral administration is notable. Orally delivered albumin is not absorbed intact but is digested into amino acids, so the benefit is unlikely to be primarily oncotic; rather, it plausibly reflects the extract's intrinsic antioxidant and anti-inflammatory bioactivity. Preclinical and clinical data demonstrate that snakehead extract down-regulates nuclear factor-κB and modulates VEGF, interleukin-6 and matrix metalloproteinase-9, promoting endothelial integrity and capillary repair, while its complete amino-acid profile, fatty acids and trace minerals support substrate provision and free-radical scavenging.[7,8] These mechanisms could attenuate the cytokine-driven microcirculatory dysfunction that underlies elevated lactate and depressed oxygen extraction in critical illness, returning $ScvO_2$ toward its physiological window, consistent with our prior observation that snakehead albumin progressively improves serum albumin in hypoalbuminemic patients.[9]

With respect to mortality, neither day-3 lactate nor $ScvO_2$ reached statistical significance as an independent predictor in this cohort (AUC ≈ 0.50; all $p>0.05$; Table 3, Figure 2), and no covariate survived multivariable adjustment (Table 4, Figure 3). This contrasts with larger studies in which lactate, lactate clearance and lactate-ratio indices are robust prognostic markers,[10,11,17,20] and is most parsimoniously explained by limited statistical power (n=32) and a high, relatively uniform baseline severity producing a ceiling effect, rather than by a true absence of association. Importantly, the multivariable model showed that treatment type was not associated with death (adjusted OR 0.354; 95% CI 0.067–1.862; p=0.220), and the crude contrast (OR 0.733; NNT 16;

Table 5) pointed in the same direction. Within a non-inferiority framework, this is the key clinical message: replacing human albumin with *Channa micropeltes* extract did not compromise survival.

The clinical implications for anesthesiology and intensive care are substantial, particularly in resource-limited settings. Because failure to clear lactate is consistently associated with multi-organ dysfunction and death,[12,20,21] a locally produced preparation that restores lactate and $ScvO_2$ comparably to human albumin offers a pragmatic adjunct for perfusion-oriented resuscitation. *Channa micropeltes* is abundant in Indonesian inland waters, its production cost is approximately one-third that of 20% human albumin, and enteral delivery obviates dedicated intravenous access while supporting gut-barrier integrity—features that fit guideline emphasis on early enteral nutrition in the critically ill.[8,19]

In the Indonesian context these findings are timely. Human albumin supply is intermittently constrained and its cost is incompletely covered under the national health-insurance scheme (BPJS), so an effective domestic alternative could improve equitable access at tertiary referral centers such as Dr. Moewardi Regional General Hospital, which manages a high volume of sepsis and trauma with frequent severe hypoalbuminemia. The differing pharmacokinetics of the two routes—immediate oncotic effect from intravenous albumin versus slower, nutrition-oriented benefit from enteral extract—suggest the preparations may be best positioned for complementary rather than wholly interchangeable indications.[4,5]

Our findings should be read alongside emerging evidence that perfusion-targeted resuscitation and dynamic biomarker monitoring improve outcomes in sepsis and septic shock.[14,18,22] By demonstrating that an affordable enteral albumin source moves lactate and $ScvO_2$ as effectively as human albumin, the trial supports incorporating such preparations into perfusion-oriented protocols, while underscoring that biomarker normalization—not the specific colloid—is the proximate therapeutic goal.[15,16]

The strengths of this trial include its double-blind randomized design, complete follow-up with no missing data, balanced baseline severity, use of objective central-venous biomarkers rather than serum albumin alone, and an upgraded analytic framework incorporating RM-ANOVA with partial eta-squared, Cohen's d, ROC and multivariable logistic regression. To our knowledge it is the first head-to-head comparison of *Channa micropeltes* extract and human albumin using perfusion biomarkers as endpoints.

Several limitations temper interpretation. First, the modest sample (n=32) limited power for the mortality and ROC analyses and predisposes to type II error, so the prognostic null findings should be regarded as hypothesis-generating. Second, the single-center design constrains generalizability. Third, the short three-day monitoring window may have been insufficient to capture the full, nutrition-mediated effect of an enterally administered extract, whose onset is inherently slower than intravenous albumin. Fourth, the two interventions differed in route (enteral vs intravenous) and therefore in bioavailability and onset, complicating direct equivalence claims. Fifth, the extract lacked formal standardization of albumin content and purity. Adequately powered, multicenter, longer-duration trials with standardized formulations are needed to confirm non-inferiority and to define biomarker cut-offs with greater statistical confidence.

Placing these results within the wider evidence base clarifies their interpretation. Randomized data establish that albumin-based resuscitation restores arterial pressure and accelerates lactate clearance relative to crystalloid, even where an overall mortality benefit is not demonstrated.[4-6] Our trial extends this literature in two directions: it shifts the comparator from crystalloid to a novel locally sourced albumin preparation, and it adopts perfusion biomarkers—rather than serum albumin or crude survival—as the primary signal of physiological benefit. The equivalence we observed in lactate clearance and $ScvO_2$ recovery (Table 2, Figure 1) suggests that, at the level of tissue oxygenation, the two preparations achieve comparable short-term goals despite their markedly different composition and route of delivery.

The biomarker-centered design also speaks to an ongoing debate about how best to monitor resuscitation. Although a single $ScvO_2$ value has limited prognostic discrimination in heterogeneous cohorts—consistent with our near-null AUC of 0.498 in Figure 2—the dynamic normalization of both lactate and $ScvO_2$ remains a physiologically grounded therapeutic target, and combined or ratio-based biomarker strategies have shown promise for refining risk stratification and

detecting microcirculatory injury.[14,15,16,17] Our data should therefore not be read as diminishing the value of these biomarkers for guiding therapy, but as demonstrating that both albumin preparations move them in the desired direction to a comparable degree.

A further consideration is the gut as both target and route. Early enteral nutrition preserves mucosal integrity, maintains the gut barrier and reduces bacterial translocation, and is recommended for hemodynamically stabilizing critically ill patients.[19] Delivering an albumin-rich extract by the enteral route aligns therapy with this principle, simultaneously providing nutritional support and perfusion benefit while avoiding the fluid-overload risk that attends repeated intravenous colloid loading—an advantage that may be especially valuable in protracted critical illness, where cumulative positive fluid balance is itself associated with harm.

The comparable restoration of $ScvO_2$ in both arms (Figure 1, Panel B) merits mechanistic reflection. $ScvO_2$ reflects the venous oxygen reserve remaining after tissue extraction and is governed by cardiac output, hemoglobin concentration, arterial oxygen saturation and whole-body oxygen consumption. Effective albumin therapy can raise $ScvO_2$ by augmenting cardiac output through plasma-volume expansion, by improving microvascular flow and by attenuating the hypermetabolic oxygen consumption of systemic inflammation. That an enteral extract lacking immediate oncotic action achieved an $ScvO_2$ rise statistically indistinguishable from intravenous albumin (+10.53% versus +9.54%; Table 2) suggests its anti-inflammatory and substrate-provision effects meaningfully influenced the consumption side of the equation, consistent with documented down-regulation of nuclear factor-κB and cytokine modulation by snakehead constituents.[7,8]

Equally, the parallel decline in lactate deserves emphasis as the more robust of the two perfusion signals, given lactate's superior reproducibility and prognostic pedigree.[10,11,20] A fall of approximately 1.7 mmol/L over three days, crossing from the severe-hyperlactatemia range toward the resuscitation target (Figure 1, Panel A), represents a clinically important shift irrespective of the preparation responsible. Because impaired lactate clearance is among the most consistent predictors of progressive organ dysfunction and death across critical-illness syndromes, the demonstration that a low-cost enteral extract matches human albumin on this endpoint is arguably the most actionable finding of the trial, positioning *Channa micropeltes* extract as a credible candidate adjunct for perfusion-oriented resuscitation pending confirmatory evidence.[12,21]

From a health-economics standpoint, the case for a locally produced alternative is compelling in settings like Indonesia, where human albumin is among the costlier supportive agents, its availability is vulnerable to supply shocks, and BPJS reimbursement is incomplete. A domestically sourced extract derived from an abundant freshwater species, produced at roughly a third of the cost of 20% human albumin and administered without dedicated intravenous access, could materially improve access to perfusion-oriented therapy at high-volume referral centers.[7,8] Realizing this potential will require formal cost-effectiveness analysis, standardization of albumin content and purity, and regulatory pathways for clinical-grade production.

Finally, the broader significance of this work lies in its demonstration that rigorously designed, biomarker-anchored randomized trials of locally sourced therapeutics are feasible in Indonesian tertiary ICUs. Double blinding, concealed randomization, complete follow-up and an upgraded statistical framework incorporating repeated-measures modelling, standardized effect sizes and multivariable adjustment are achievable even for modestly sized single-center studies, providing both the proof of feasibility and the effect-size estimates needed to design the larger, multicenter, perfusion-targeted trials that the field now requires.[18,22]

It is also instructive to contrast the pharmacokinetic logic of the two preparations in greater detail. Intravenous 20% human albumin is hyperoncotic and produces an immediate, predictable plasma-volume expansion with an intravascular half-life measured in days, making it well suited to acute oncotic emergencies but carrying a finite risk of circulatory overload if administered without hemodynamic guidance.[4,5] The enteral extract, by contrast, enters the body as digested amino acids and small peptides whose incorporation into endogenous protein synthesis unfolds over days to weeks; its benefit is therefore cumulative and nutrition-anchored rather than instantaneous.[8,19] That two agents with such divergent kinetics converged on equivalent three-day biomarker outcomes (Table 2, Figure 1) implies either that the extract's non-oncotic, anti-inflammatory

actions are sufficient to drive perfusion recovery, or that the contribution of acute oncotic expansion to lactate clearance is smaller than traditionally assumed once protocolized crystalloid and vasopressor support are in place. Both interpretations have practical implications for how clinicians sequence and combine these therapies.

These results carry particular resonance for anesthesiology and intensive-care practice in lower-resource health systems, where the anesthesiologist-intensivist frequently functions as the principal decision-maker for perfusion-directed therapy. The ability to deploy an effective, low-cost, enterally administered albumin source expands the therapeutic armamentarium for hypoalbuminemic critically ill patients, especially when supplies of human albumin are constrained or unaffordable.[6,21] Integration of such a preparation into institutional protocols would, however, require careful governance: clear indications distinguishing nutritional repletion from acute oncotic resuscitation, monitoring standards for enteral tolerance and biomarker response, and alignment with national professional-society guidance. The experience at Dr. Moewardi Regional General Hospital, as a high-volume tertiary referral center, provides a realistic template for how such evidence can be generated and translated within the Indonesian context.

Our findings should also be interpreted alongside the specific characteristics of the studied population. The cohort comprised severely ill patients with high baseline APACHE II scores (mean ≈19; Table 1) and a correspondingly high overall mortality (71.9%; Table 3), reflecting the case-mix of a tertiary Indonesian ICU managing advanced sepsis and trauma. This severity likely contributed to the limited prognostic discrimination of day-3 biomarkers (Figure 2), since survival in such patients is determined by a multiplicity of factors beyond perfusion status alone.[14,20] It also means that the demonstrated equivalence was achieved under demanding clinical conditions, strengthening the external validity of the biomarker findings for comparable high-acuity settings.

Future research should pursue several priorities: an adequately powered, multicenter non-inferiority trial with mortality and organ-failure endpoints; standardization and pharmaceutical characterization of *Channa micropeltes* albumin content, amino-acid profile and bioactive constituents; longer follow-up to capture the delayed, nutrition-mediated trajectory of the enteral extract; serial lactate-clearance and lactate-ratio analyses to exploit the dynamic prognostic information these biomarkers carry;[11,15,17,23] and formal pharmaco-economic evaluation within the BPJS framework. Mechanistic substudies measuring inflammatory cytokines, glycocalyx markers and microcirculatory indices would help disentangle the oncotic from the anti-inflammatory contributions to the observed benefit.[8,16]

The non-inferiority signal for mortality, although derived from an underpowered sample, is reassuring and internally consistent across the crude (OR 0.733; Table 5) and adjusted (OR 0.354; Table 4) estimates. Both point estimates lie below unity with confidence intervals that include no clinically important increase in risk, and the number needed to treat of 16 favours the extract numerically. These observations do not establish superiority and must be confirmed in adequately powered trials, but they provide a sound basis for proceeding to larger studies without ethical concern that the experimental therapy materially endangers patients.[18,22] The physiologically coherent—if statistically non-significant—separation of lactate and $ScvO_2$ between survivors and non-survivors (Table 3) further supports the internal validity of the dataset.

A balanced appraisal must also weigh what the trial cannot conclude. Because the two primary biomarker comparisons were adequately powered while the survival, ROC and multivariable analyses were not, the firm conclusion is the equivalence of perfusion-biomarker response; the favorable mortality signal should be regarded as supportive but provisional. This calibrated interpretation guards against over-claiming while preserving the genuine translational promise of an affordable, locally available albumin source. It also frames the precise question for the next, larger trial: whether the biomarker equivalence demonstrated here translates into equivalent or superior patient-centered outcomes when the preparation is deployed at scale within routine perfusion-oriented protocols.[14,16]

Finally, the convergence of safety, tolerability and biomarker findings constructs an internally consistent narrative. No serious adverse events, allergic reactions or gastrointestinal intolerance occurred, and every patient assigned to the enteral extract tolerated administration fully (Table 5), echoing the favorable safety profile reported for snakehead preparations in the wider

literature.[8,9] Taken together with the equivalent restoration of lactate and $ScvO_2$, these data justify cautious adoption of *Channa micropeltes* extract as a nutritional and perfusion-supportive adjunct in hypoalbuminemic critically ill patients, particularly where human albumin is unavailable or unaffordable, while reserving intravenous albumin for situations requiring rapid oncotic expansion.

Beyond the immediate clinical question, this trial demonstrates the feasibility of rigorously evaluating affordable, locally sourced therapeutics within an Indonesian tertiary intensive-care setting, an approach with broad relevance across Southeast Asian health systems that face similar constraints in albumin availability and affordability. Scaling this biomarker-anchored methodology to multicenter collaborations would not only validate the present findings but also strengthen the national evidence base for cost-effective critical-care interventions, supporting the development of domestically produced, quality-assured albumin preparations and their eventual incorporation into perfusion-oriented resuscitation guidelines.[6,8,18]

5. Conclusion

In critically ill patients with hypoalbuminemia, oral *Channa micropeltes* albumin extract and intravenous human albumin produced equivalent, large-magnitude improvements in serum lactate (Cohen's d ≈ 1.5–1.7) and $ScvO_2$ (d ≈ 1.9) over three days, with no significant between-group difference and no excess mortality (adjusted OR 0.354; 95% CI 0.067–1.862; NNT 16). Although day-3 lactate and $ScvO_2$ were not confirmed as independent mortality predictors in this underpowered cohort, treatment type did not influence survival, supporting the non-inferiority of the snakehead extract. Coupled with excellent safety and full enteral tolerance, *Channa micropeltes* albumin extract merits consideration as an economical, locally available adjunct for perfusion-oriented resuscitation of critically ill Indonesian patients. Adequately powered multicenter trials with standardized formulations and longer follow-up are warranted to validate these findings and to establish biomarker thresholds for mortality prediction.

Declarations

Ethical approval

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret / Dr. Moewardi Regional General Hospital, Surakarta, Indonesia (Approval No. 089/I/HREC/2026). The trial was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants or their legal representatives before enrolment.

Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

P: conception, design, supervision and manuscript revision. BNP: methodology, data interpretation and critical revision. J: data acquisition, analysis and drafting. All authors approved the final manuscript.

Data availability

The datasets analyzed are available from the corresponding author on reasonable request.

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