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Serial Serum Albumin Estimation as a Prognostic Marker in Critically Ill Patients: A Prospective Observational Study from a Tertiary Care Hospital in Central India

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Abstract

Background: Serum albumin falls in critical illness and predicts mortality, but the value of serial measurements in Indian intensive care units (ICUs) is unclear. We evaluated serial serum albumin as a prognostic marker in critically ill adults. **Materials and Methods:** In this prospective observational study, 200 consecutive adults admitted to a tertiary ICU in Bhopal, India, had serum albumin measured on Day 1, Day 3, and Day 5. Severity was scored with the Acute Physiology and Chronic Health Evaluation II (APACHE II). Albumin levels, categories, and trends were compared between survivors and non-survivors (t-test, Chi-square test, relative risk [RR], and odds ratio [OR]). **Results:** Mortality was 24.0% (48/200), and 62.5% had hypoalbuminemia (<3.5 g/dL) on admission. Non-survivors had lower albumin than survivors at every time point (Day 1: 2.38 ± 0.82 vs. 3.38 ± 0.71 g/dL; Day 5: 2.29 ± 0.85 vs. 3.37 ± 0.71 g/dL; $P < 0.001$). Mortality rose from 9.3% with normal albumin to 60.0% with albumin <2.5 g/dL (P for trend <0.001; RR 6.43, 95% confidence interval [CI] 2.96–13.95). A deteriorating albumin trend carried an OR of 5.87 (95% CI 1.98–17.35) versus an improving trend. Albumin was lower in patients needing vasopressors but did not correlate with APACHE II score. **Conclusion:** Low and declining serum albumin was associated with higher mortality. Serial albumin estimation is inexpensive and may complement clinical assessment in resource-limited ICUs; multicenter studies with multivariable adjustment are needed.

Keywords: Critical illness, Hypoalbuminemia, Intensive care units, Mortality, Prognosis, Serum albumin

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Introduction

Critically ill patients admitted to the intensive care unit (ICU) remain at high risk of death despite advances in monitoring and organ support.[1,2] Early identification of patients likely to deteriorate allows timely escalation of care and better use of scarce resources. Scoring systems such as the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) are widely used to grade severity,[3] but they depend on many physiological and laboratory variables, and simple, inexpensive biochemical markers are attractive complements, particularly in resource-limited settings.

Albumin is the most abundant plasma protein. It is synthesized by the liver, has a normal serum concentration of about 3.5–5.0 g/dL, maintains colloid oncotic pressure, and transports hormones, fatty acids, bilirubin, calcium, and many drugs.[4,5] It also has antioxidant, anti-inflammatory, and endothelium-protective properties.[5,6]

In acute illness, serum albumin often falls. Contributing mechanisms include inflammation-driven suppression of hepatic synthesis, increased capillary permeability with transcapillary escape, dilution after fluid resuscitation, and enhanced catabolism [Figure 1].[7,8] Hypoalbuminemia in this setting mainly reflects inflammation and disease severity rather than nutritional deficiency alone,[8,9] and has been associated with higher mortality, morbidity and longer ICU stay in a meta-analysis and in several cohort studies.[8,10-13]

A single admission value may not capture the dynamic changes of critical illness. Serial measurements and albumin trends have been reported to carry prognostic information,[14-16] and combining albumin with severity scores such as SOFA has been explored to refine risk stratification.[17,18] Data from India are limited, although sepsis alone affects more than half of ICU patients in a national point-prevalence study,[19] and regional differences in disease pattern, nutrition, and health-care infrastructure argue for locally generated evidence.[20]

We, therefore, studied serial serum albumin (Day 1, Day 3, and Day 5) as a prognostic marker in critically ill adults in a tertiary ICU in central India. Our objectives were to (i) compare albumin levels between survivors and non-survivors, (ii) relate albumin category and trend to mortality, and (iii) examine the association of albumin with disease severity, organ support, and length of ICU stay.

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Materials and Methods

Study Design, Setting, and Ethics

This was a single-center, hospital-based, prospective observational study conducted in the ICU of the Department of Medicine, L.N. Medical College and Research Centre and J.K. Hospital, Bhopal, Madhya Pradesh, India, a tertiary facility offering mechanical

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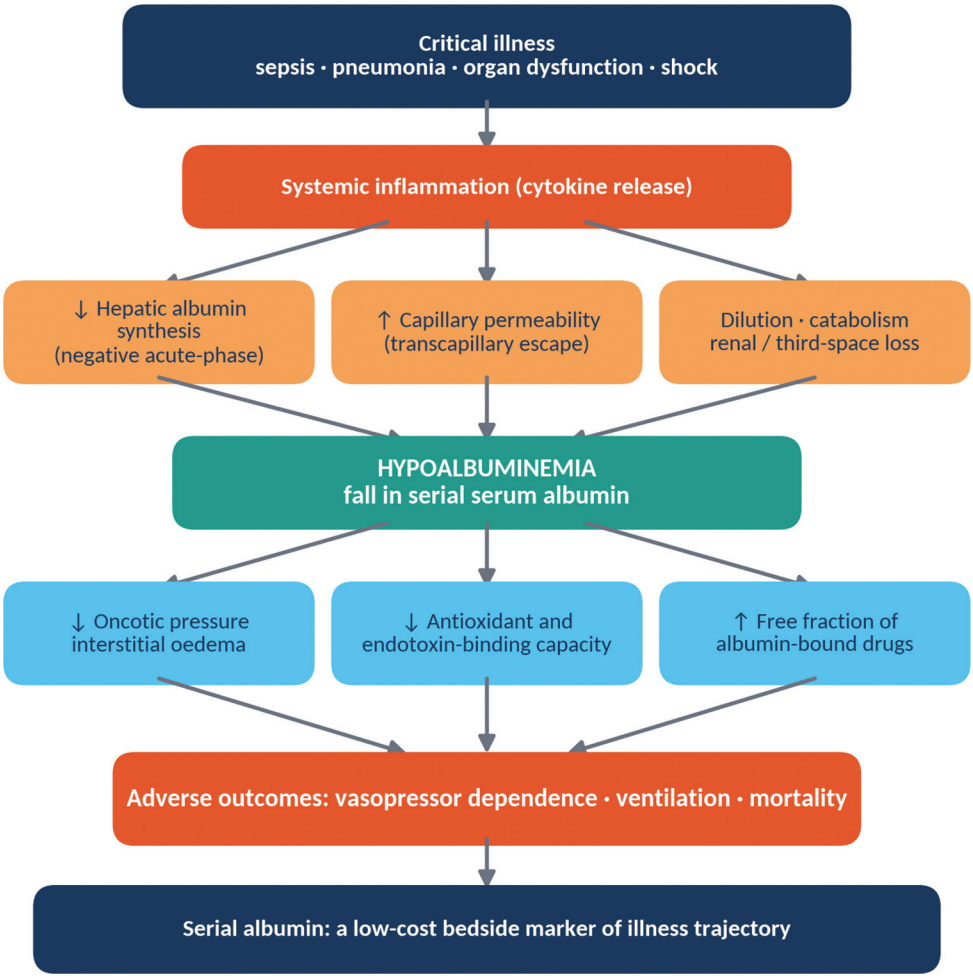


Figure 1: Conceptual framework linking critical illness, hypoalbuminemia, and adverse outcomes. Systemic inflammation lowers serum albumin through reduced hepatic synthesis, increased capillary permeability, and dilution or loss; hypoalbuminemia is in turn associated with reduced oncotic pressure, antioxidant capacity and altered drug binding, and with vasopressor dependence, ventilation, and death

ventilation, inotropic and vasopressor support, hemodialysis, and parenteral nutrition. The study spanned 18 months: a 3-month planning phase, a 12-month phase of recruitment and data collection, and a 3-month phase of analysis and reporting. The Institutional Ethics Committee of L.N. Medical College and Research Center approved the protocol before data collection began. The study followed the Declaration of Helsinki, and written informed consent was obtained from all participants or their legal guardians.

Participants

All patients admitted to the ICU during the study period formed the study universe. Critically ill patients were defined as those with dysfunction or failure of one or more organ systems, at increased risk of death or major morbidity without intervention, and dependent on advanced monitoring or therapy such as mechanical ventilation, inotropic or vasopressor support, hemodialysis, parenteral nutrition, or close airway monitoring. Adults aged 18 years or older who required critical care support and gave written informed consent were eligible. We excluded patients with chronic liver disease, chronic kidney disease with proteinuria, or other pre-existing chronic disease likely to alter albumin metabolism; patients who died within 3 days of admission (serial sampling could not be completed); and those who declined consent [Figure 2].

Sample size was estimated with Slovin's formula, $n = N/(1 + Ne^2)$, with a margin of error (e) of 0.05, and 200 patients were enrolled after considering feasibility and the study duration. Patients were recruited by consecutive sampling until this number was reached.

Data Collection and Severity Assessment

A structured pro forma recorded demographic details (age, sex, education, occupation, residence, and socio-economic status), presenting complaints, past and personal history, and general and systemic examination. Baseline investigations on Day 1 included complete blood count, liver and renal function tests, serum electrolytes, blood glucose, glycated hemoglobin, arterial blood gas analysis, urine examination, coagulation profile, and chest radiograph. Severity of illness was graded with the APACHE II score and categorized as low (<15), moderate (15–24), or high (>24) risk.

Serum Albumin Estimation

Venous blood (5 mL) was drawn under aseptic precautions on Day 1 (admission), Day 3, and Day 5 after admission. Samples

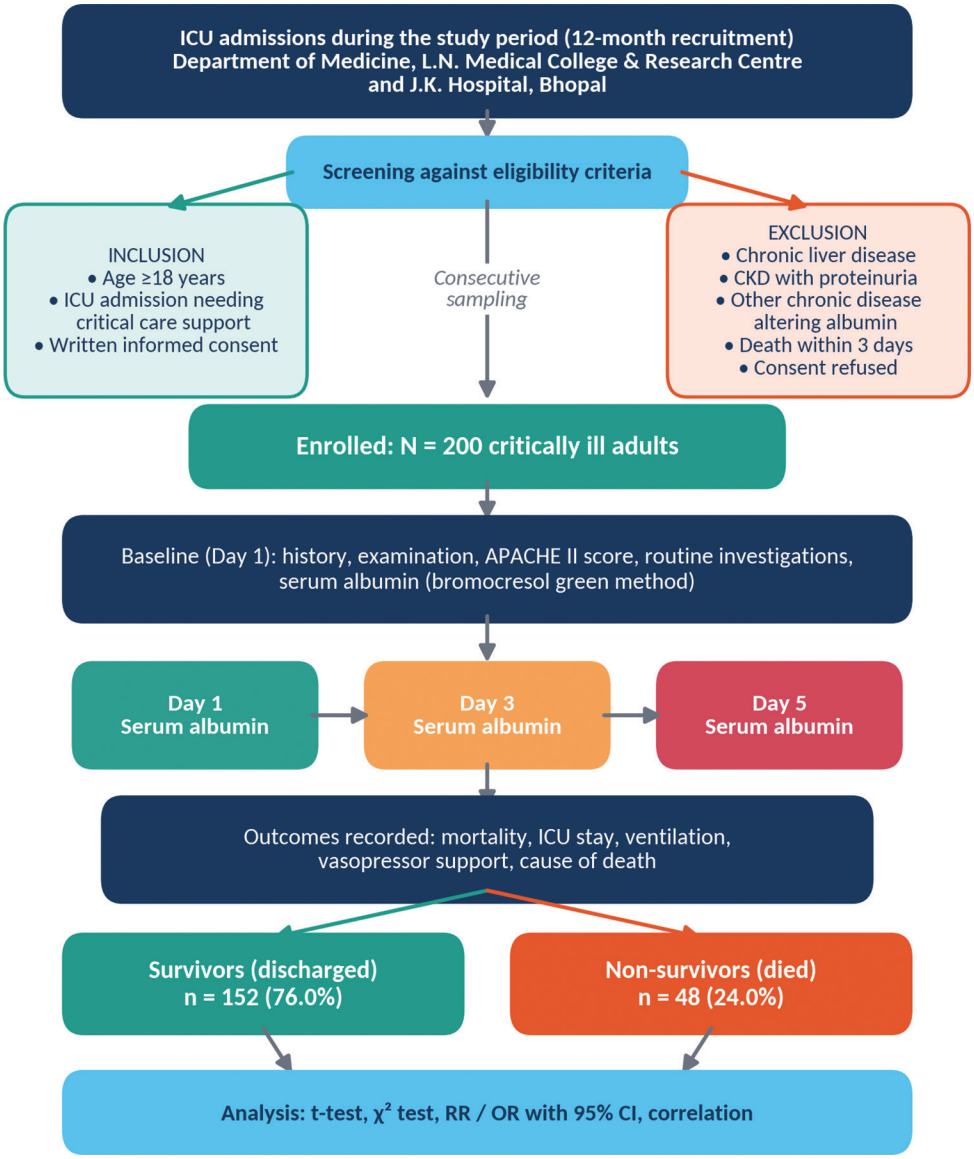


Figure 2: Flow chart of the study. Consecutive ICU admissions were screened against eligibility criteria and 200 critically ill adults were enrolled. Serum albumin was measured on Day 1, Day 3, and Day 5, and outcomes were classified as survivors ($n = 152$) or non-survivors ($n = 48$). ICU: Intensive care unit, CKD: Chronic kidney disease, APACHE II: Acute Physiology and Chronic Health Evaluation II, RR: Relative risk, OR: odds ratio

were allowed to clot at room temperature and centrifuged at 3000 rpm for 10 min, and serum was analyzed on a fully automated Biosystems BS-430 analyzer using the bromocresol green dye-binding method, in which albumin forms a colored complex in acid medium that is measured spectrophotometrically.[21] The reference range was 3.5–5.0 g/dL. Albumin was categorized as normal (≥3.5 g/dL), mild (3.0–3.4 g/dL), moderate (2.5–2.9 g/dL), or severe (<2.5 g/dL) hypoalbuminemia, and hypoalbuminemia was defined as a value below 3.5 g/dL [Figure 3]. Change between Day 1 and Day 5 was classified as an improving, static, or deteriorating trend.

Outcomes

The primary outcome was mortality (death vs. discharge). Secondary outcomes were length of ICU stay, need for mechanical ventilation, need for vasopressor support, and cause of death.

Statistical Analysis

Data were entered in Microsoft Excel 2021 and analyzed in R version 4.5.1. Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and percentages. Albumin values were compared between survivors and non-survivors, and between other two-group comparisons, with the independent t-test; within-group change was tested with the paired t-test, and comparisons across three groups used one-way analysis of variance. Categorical variables were compared with the Chi-square test (Fisher's exact test when expected counts were below 5), and the Chi-square test for trend was used across ordered albumin categories. Relative risk (RR) and odds ratio (OR) with 95% confidence intervals (CI) were calculated using the lowest-risk category as reference. Pearson's and Spearman's coefficients assessed the correlation between APACHE II score and albumin. A two-sided *P* value below 0.05 was considered significant. Each

participant received a unique identification number, and records were stored de-identified with access restricted to the investigators.

Results

Study Population

Two hundred critically ill adults were enrolled [Figure 2]. Their mean age was 57.2 ± 17.3 years (range 18–88); 44.0% were older than 60 years, 57.0% were men, and 60.0% lived in urban areas [Table 1 and Figure 4]. Hypertension (39.5%) and diabetes mellitus (29.5%) were the most common comorbidities, and 38.0% had none. The mean APACHE II score was 18.1 ± 7.5, with 29.5%, 51.0%, and 19.5% of patients in the low-, moderate-, and high-risk categories. Mechanical ventilation was needed in 37.5% and vasopressor support in 40.5%; the mean ICU stay was 6.9 ± 5.8 days (median 5, interquartile range 3–8).

Sepsis (25.5%), pneumonia (10.5%), chronic obstructive pulmonary disease exacerbation (7.5%), and stroke (7.5%) were the most common primary diagnoses [Table 2]. Overall, mortality was 24.0% (48/200); 40 of the 48 deaths (83.3%) were sepsis-related (sepsis 26, pneumonia 10, and urinary tract infection 4) and eight were non-sepsis deaths (stroke 3, pulmonary embolism 3, and decompensated heart failure 2). Non-survivors were more often

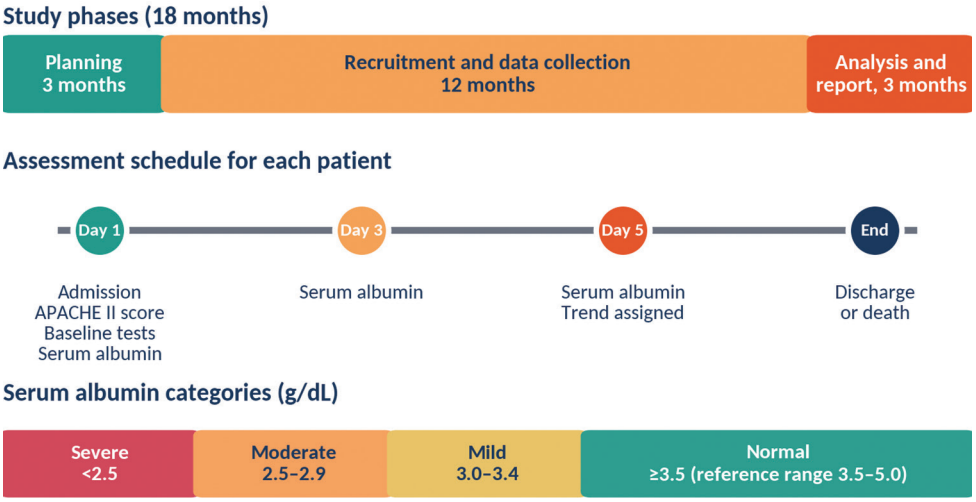


Figure 3: Study timeline and albumin classification. Top, phases of the 18-month study. Middle, assessment schedule for each patient: serum albumin on Day 1 (admission), Day 3 and Day 5, with the outcome recorded as discharge or death. Bottom, categories of serum albumin (g/dL) used in the analysis. APACHE II: Acute Physiology and Chronic Health Evaluation II

Table 1: Baseline characteristics of the study population and comparison between survivors and non-survivors

Characteristic	*All patients (n=200)*	*Survivors (n=152)*	*Non-survivors (n=48)*	*P-value*[a]
Demographic profile				
Age, years, mean±SD	57.2±17.3	56.9±17.7	58.1±16.1	0.690
Age >60 years, *n* (%)	88 (44.0)	67 (44.1)	21 (43.8)	0.968
Male sex, *n* (%)	114 (57.0)	85 (55.9)	29 (60.4)	0.583
Urban residence, *n* (%)	120 (60.0)	95 (62.5)	25 (52.1)	0.199
Socio-economic status, *n* (%)				0.301
Upper class	18 (9.0)	15 (9.9)	3 (6.3)	
Middle class	110 (55.0)	79 (52.0)	31 (64.6)	
Lower class	72 (36.0)	58 (38.2)	14 (29.2)	
Comorbidities				
Diabetes mellitus, *n* (%)	59 (29.5)	53 (34.9)	6 (12.5)	**0.003**
Hypertension, *n* (%)	79 (39.5)	69 (45.4)	10 (20.8)	**0.002**
Thyroid disorder, *n* (%)	28 (14.0)	21 (13.8)	7 (14.6)	0.894
No comorbidity, *n* (%)	76 (38.0)	47 (30.9)	29 (60.4)	**<0.001**
Severity, organ support, and diagnosis				
APACHE II score, mean±SD	18.1±7.5	17.7±7.3	19.4±7.9	0.169
APACHE II category, *n* (%)				0.314
Low risk (<15)	59 (29.5)	46 (30.3)	13 (27.1)	
Moderate risk (15–24)	102 (51.0)	80 (52.6)	22 (45.8)	
High risk (>24)	39 (19.5)	26 (17.1)	13 (27.1)	
Mechanical ventilation, *n* (%)	75 (37.5)	48 (31.6)	27 (56.3)	**0.002**
Vasopressor support, *n* (%)	81 (40.5)	52 (34.2)	29 (60.4)	**0.001**
ICU stay, days, mean±SD	6.9±5.8	6.8±5.7	7.0±6.2	0.871
Sepsis-related diagnosis[b], *n* (%)	82 (41.0)	42 (27.6)	40 (83.3)	**<0.001**

SD: Standard deviation, APACHE II: Acute physiology and chronic health evaluation II, ICU: Intensive care unit. [a]Independent t-test for continuous variables; Chi-square test for categorical variables (row-wise for socio-economic status and APACHE II category); values below 0.05 are highlighted. [b]Sepsis, pneumonia, or urinary tract infection as primary diagnosis. Bold values indicate *P*<0.05

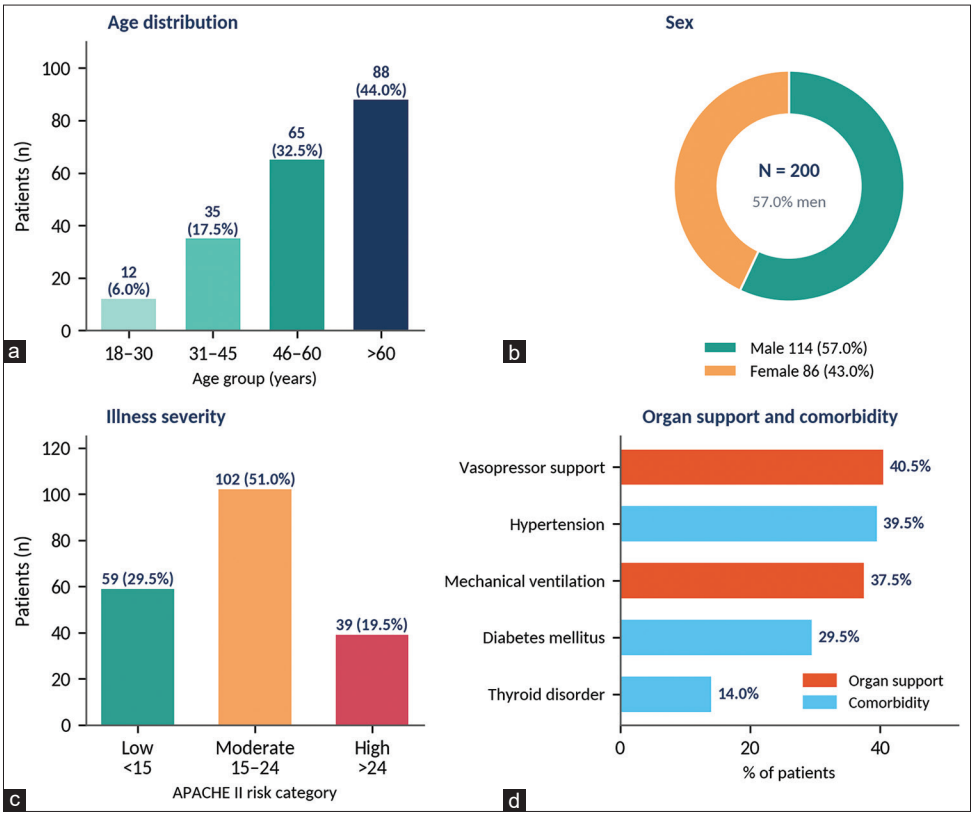


Figure 4: Baseline profile of the 200 patients. (a) Age distribution. (b) Sex. (c) APACHE II risk category. (d) Percentage of patients who needed vasopressor support or mechanical ventilation and who had common comorbidities. APACHE II: Acute Physiology and Chronic Health Evaluation II

Table 2: Primary diagnosis, mortality, and admission (Day 1) serum albumin

Primary diagnosis	*Patients, n (%)*	*Deaths, n*	*Mortality, %*	*Day 1 albumin, g/dL (mean±SD)*
Sepsis-related diagnoses (82 patients, 40 deaths)				
Sepsis/septic shock	51 (25.5)	26	51.0	2.77±0.89
Pneumonia	21 (10.5)	10	47.6	3.05±0.98
Urinary tract infection	10 (5.0)	4	40.0	2.74±0.89
Other diagnoses (118 patients, eight deaths)				
Chronic obstructive pulmonary disease exacerbation	15 (7.5)	0	0.0	3.36±0.47
Stroke	15 (7.5)	3	20.0	3.18±0.83
Guillain-Barré syndrome	12 (6.0)	0	0.0	3.37±0.63
Acute pancreatitis	10 (5.0)	0	0.0	3.35±0.54
Decompensated heart failure	10 (5.0)	2	20.0	2.89±0.76
Acute severe asthma	8 (4.0)	0	0.0	2.92±0.90
Diabetic ketoacidosis	8 (4.0)	0	0.0	3.97±0.66
Pulmonary embolism	8 (4.0)	3	37.5	3.10±0.80
Hypertensive emergency	7 (3.5)	0	0.0	3.56±0.89
Adrenal crisis	6 (3.0)	0	0.0	3.62±0.68
Organophosphate poisoning	6 (3.0)	0	0.0	3.65±0.83
Meningitis	5 (2.5)	0	0.0	3.64±0.39
Snake envenomation	5 (2.5)	0	0.0	3.80±0.96
Seizure disorder	3 (1.5)	0	0.0	3.14±0.42

Percentages of patients are calculated from *n*=200

ventilated and on vasopressors and more often had a sepsis-related diagnosis, whereas age, sex, APACHE II score, and ICU stay did not differ significantly [Table 1].

Key finding

Nearly half (44.0%) of patients were older than 60 years, most were moderately to severely ill, and 83.3% of deaths were sepsis-related.

Serial Serum Albumin and Outcome

Mean serum albumin was 3.14 ± 0.85 g/dL on Day 1, 3.12 ± 0.87 g/dL on Day 3, and 3.11 ± 0.88 g/dL on Day 5 [Table 3]. Non-survivors had significantly lower albumin than survivors at all three time points (Day 1: 2.38 ± 0.82 vs. 3.38 ± 0.71 g/dL; Day 3: 2.31 ± 0.83 vs. 3.38 ± 0.71 g/dL; and Day 5: 2.29 ± 0.85 vs. 3.37 ± 0.71 g/dL; $P < 0.001$ for each) [Figure 5]. The mean fall from Day 1 to Day 5

Table 3: Serial serum albumin (g/dL) in all patients, survivors and non-survivors

Time point	*All patients (n=200)*	*Survivors (n=152)*	*Non-survivors (n=48)*	*P-value*[a]
Day 1	3.14±0.85	3.38±0.71	2.38±0.82	<0.001
Day 3	3.12±0.87	3.38±0.71	2.31±0.83	<0.001
Day 5	3.11±0.88	3.37±0.71	2.29±0.85	<0.001
Change, Day 1–Day 5[b]	−0.03±0.09	−0.01±0.07	−0.09±0.09	<0.001[c]
Within-group *P* value[d]	<0.001	0.034	<0.001	

Values are mean±SD. [a]Independent t-test, survivors versus non-survivors. [b]Day 5 minus Day 1. [c]Independent t-test comparing change between survivors and non-survivors. [d]Paired t-test, Day 5 versus Day 1

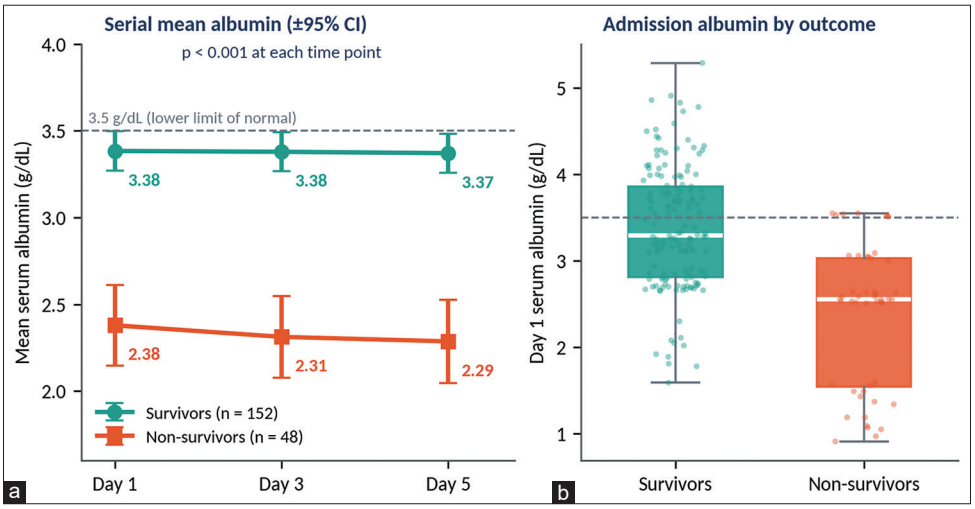


Figure 5: Serum albumin in survivors and non-survivors. (a) Mean serum albumin (with 95% confidence intervals) on Day 1, Day 3, and Day 5; non-survivors had significantly lower values at every time point ($P < 0.001$). (b) Distribution of Day 1 albumin by outcome; boxes show the median and interquartile range, points are individual patients and the dashed line marks 3.5 g/dL

was small overall (−0.03 g/dL), but was larger in non-survivors (−0.09 g/dL, $P < 0.001$) than in survivors (−0.01 g/dL, $P = 0.034$); the difference in change between the two groups was significant ($P < 0.001$).

Hypoalbuminemia (<3.5 g/dL) affected 62.5% of patients on Day 1, 64.5% on Day 3, and 64.5% on Day 5, and severe hypoalbuminemia (<2.5 g/dL) increased from 12.5% to 17.5% and 19.0% [Table 4]. Individual trajectories and category shifts are shown in Figure 6: 174 patients (87.0%) remained in the same category from Day 1 to Day 5, 24 (12.0%) moved to a lower category and 2 (1.0%) to a higher one.

Key finding

Non-survivors began lower (2.38 vs. 3.38 g/dL) and stayed lower on every day (all $P < 0.001$), with a larger fall by Day 5.

Albumin Category, Trend, and Mortality

Mortality increased stepwise with the severity of admission hypoalbuminemia: 9.3% (7/75) with normal albumin, 16.7% (7/42) with mild, 32.8% (19/58) with moderate, and 60.0% (15/25) with severe hypoalbuminemia (Chi-square for trend, $P < 0.001$) [Table 5 and Figure 7a]. Compared with normal albumin, the RR of death was 3.51 (95% CI 1.58–7.78) for moderate and 6.43 (95% CI 2.96–13.95) for severe hypoalbuminemia, whereas the estimate for mild hypoalbuminemia was imprecise (RR 1.79; 95% CI 0.67–4.74) [Figure 8].

Albumin trend from Day 1 to Day 5 was also associated with outcome [Table 6 and Figure 7b]. Among survivors, 28.9% had an improving, 51.3% a static and 19.7% a deteriorating trend, compared with 10.4%, 47.9%, and 41.7% of non-survivors (Chi-square $P = 0.002$). Mortality was 10.2% with an improving, 22.8% with a static and 40.0% with a deteriorating trend. Relative to an improving trend, the OR of death was 5.87 (95% CI 1.98–17.35) for a deteriorating trend and 2.59 (95% CI 0.92–7.31) for a static trend. Cross-classifying Day 1 category and trend showed a gradient in both directions [Figure 9]: Mortality ranged from 5% (1/21) with normal albumin and an improving trend to 78% (7/9) with severe hypoalbuminemia and a deteriorating trend, although several cells contained few patients.

Key finding

Mortality climbed from 9.3% to 60.0% as albumin fell, and a deteriorating trend carried an OR of 5.87 for death.

Organ Support, ICU Stay, and Disease Severity

Albumin was lower in patients who needed vasopressors, significantly so at every time point (Day 1: 2.94 ± 0.87 vs. 3.28 ± 0.81 g/dL, $P = 0.007$; and Day 5: 2.90 ± 0.89 vs. 3.26 ± 0.84 g/dL, $P = 0.004$), and mortality was higher in this group (35.8% vs. 16.0%; $P = 0.001$) [Table 7].. Mechanically ventilated patients had albumin levels similar to non-ventilated patients but significantly higher mortality (36.0% vs. 16.8%; $P = 0.002$).

Albumin did not differ significantly across APACHE II risk categories (Day 1 $P = 0.688$; and Day 5 $P = 0.761$) and showed no correlation with the APACHE II score (Day 1: r = −0.01, $P = 0.88$; and Day 5: r = −0.02, $P = 0.79$) [Table 8 and Figure 10]. Albumin also did not differ significantly by length of ICU stay or socio-economic class, and mortality did not differ across these strata.

Table 4: Distribution of serum albumin categories on Day 1, Day 3, and Day 5

Albumin category (g/dL)	*Day 1, n (%)*	*Day 3, n (%)*	*Day 5, n (%)*
Normal (≥3.5)	75 (37.5)	71 (35.5)	71 (35.5)
Mild (3.0–3.4)	42 (21.0)	43 (21.5)	41 (20.5)
Moderate (2.5–2.9)	58 (29.0)	51 (25.5)	50 (25.0)
Severe (<2.5)	25 (12.5)	35 (17.5)	38 (19.0)
Any hypoalbuminemia (<3.5)	125 (62.5)	129 (64.5)	129 (64.5)

Percentages are calculated from *n*=200 at each time point

Table 5: Mortality according to Day 1 serum albumin category

Day 1 albumin category (g/dL)	*Patients, n*	*Deaths, n*	*Mortality, %*	*RR (95% CI)[a]*
Normal (≥3.5)	75	7	9.3	1.00 (reference)
Mild (3.0–3.4)	42	7	16.7	1.79 (0.67–4.74)
Moderate (2.5–2.9)	58	19	32.8	3.51 (1.58–7.78)
Severe (<2.5)	25	15	60.0	6.43 (2.96–13.95)
Any hypoalbuminemia (<3.5)	125	41	32.8	3.51 (1.66–7.43)

RR: Relative risk, CI: Confidence interval. [a]Relative to normal albumin. Overall Chi-square $P<0.001$; Chi-square for trend $P<0.001$

Key finding

Albumin was lower in patients needing vasopressors but did not track APACHE II score, ICU stay, or socio-economic class.

Findings by Primary Diagnosis

All deaths occurred in six diagnostic groups [Figure 11]. Within each of them, non-survivors had lower albumin at every time point, and in five of the six groups (all except pulmonary embolism) a larger fall from Day 1 to Day 5 than survivors [Table 9]; numbers in the non-sepsis groups were too small for formal testing.

Discussion

Principal Findings

In this prospective study of 200 critically ill adults, serum albumin was consistently lower in non-survivors than in survivors on Day 1, Day 3, and Day 5, and mortality rose in a graded fashion from 9.3% with normal albumin to 60.0% with severe hypoalbuminemia (<2.5 g/dL). Patients whose albumin deteriorated over the first 5 days had close to six-fold higher odds of death than those whose albumin improved, and albumin was lower in patients requiring vasopressors. These observations are consistent with the view that albumin is a readily available marker of the inflammatory burden and physiological reserve of the critically ill patient [Figure 1].

Table 6: Association between albumin trend (Day 1–Day 5) and outcome

Albumin trend	*Patients, n*	*Survivors, n (%)*	*Non-survivors, n (%)*	*Mortality, %*	*OR (95% CI)[a]*
Improving	49	44 (28.9)	5 (10.4)	10.2	1.00 (reference)
Static	101	78 (51.3)	23 (47.9)	22.8	2.59 (0.92–7.31)
Deteriorating	50	30 (19.7)	20 (41.7)	40.0	5.87(1.98–17.35)

OR: Odds ratio, CI: Confidence interval. [a]Relative to improving trend. Overall Chi-square $P=0.002$

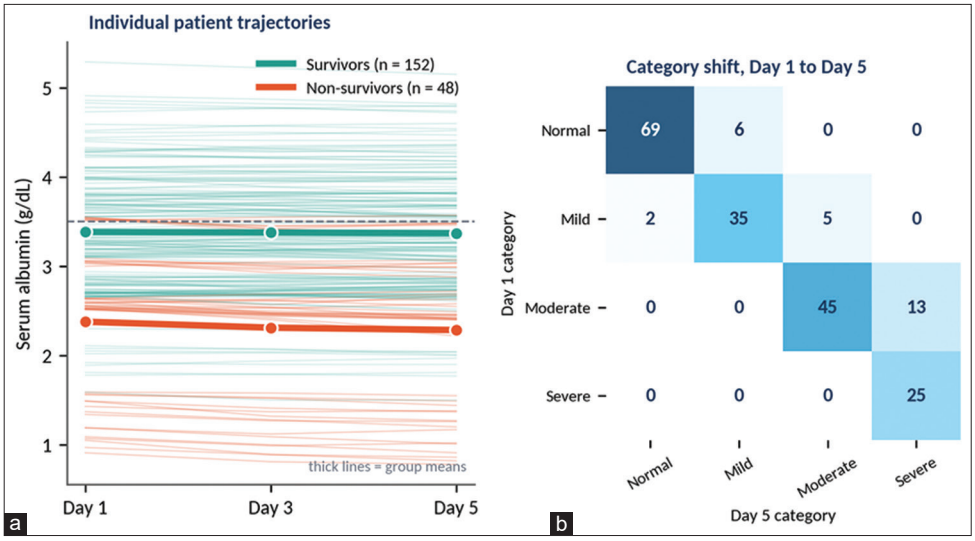


Figure 6: Individual trajectories and category shifts. (a) Serum albumin trajectories of individual patients (thin lines) with group means (thick lines); the dashed line marks 3.5 g/dL. (b) Number of patients in each albumin category on Day 1 (rows) and Day 5 (columns): 174 patients (87.0%) stayed in the same category, 24 (12.0%) moved to a lower category, and 2 (1.0%) to a higher category

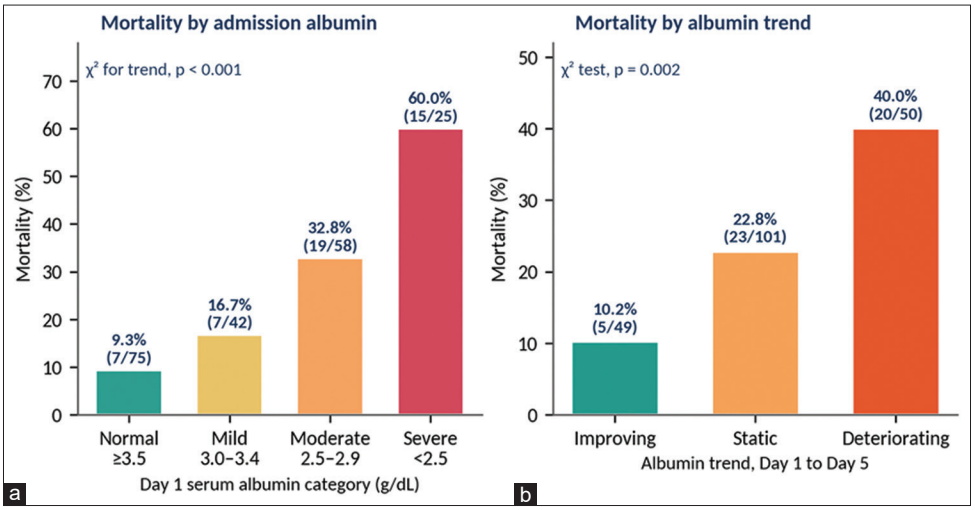


Figure 7: Mortality by albumin category and trend. (a) Mortality according to Day 1 albumin category (Chi-square for trend, $P < 0.001$). (b) Mortality according to albumin trend from Day 1 to Day 5 (Chi-square test, $P = 0.002$). Labels show percentage (deaths/patients)

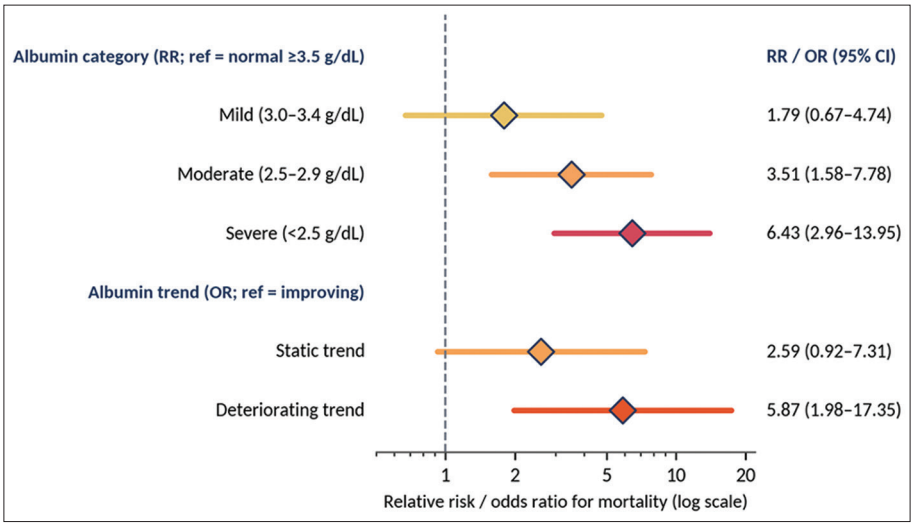


Figure 8: Forest plot of mortality risk. Relative risk of death for mild, moderate and severe hypoalbuminemia relative to normal Day 1 albumin, and odds ratio of death for static and deteriorating trends relative to an improving trend. Horizontal lines show 95% confidence intervals; the dashed line marks no association (1.0); the axis is logarithmic

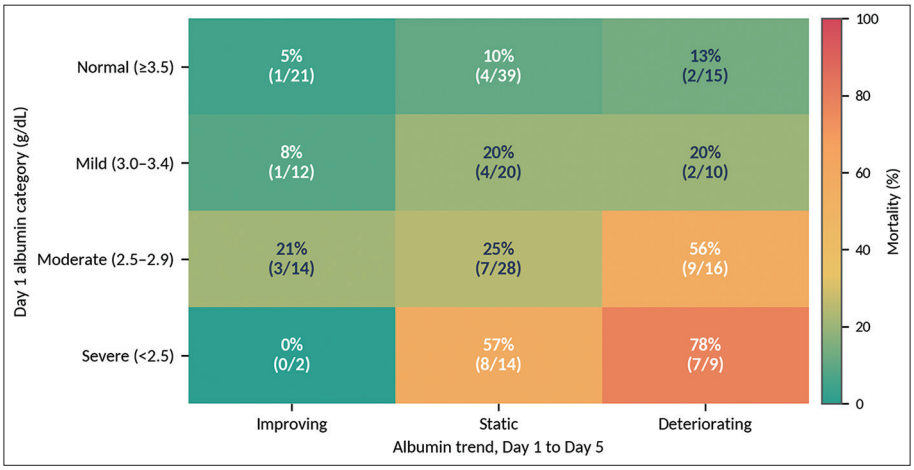


Figure 9: Mortality by Day 1 albumin category and albumin trend. Each cell shows mortality (%) with deaths/patients in parentheses. The analysis is descriptive; several cells contain few patients and their estimates are imprecise

Table 7: Serum albumin, hypoalbuminemia, and mortality according to vasopressor and ventilatory support

Parameter	*Vasopressor: Yes (n=81)*	*Vasopressor: No (n=119)*	*P*[a]	*Ventilation: Yes (n=75)*	*Ventilation: No (n=125)*	*P*[a]
Serum albumin, g/dL (mean±SD)						
Day 1	2.94±0.87	3.28±0.81	0.007	3.05±0.86	3.20±0.84	0.248
Day 3	2.91±0.89	3.26±0.83	0.005	3.03±0.88	3.18±0.86	0.232
Day 5	2.90±0.89	3.26±0.84	0.004	3.01±0.88	3.17±0.87	0.227
Categorical outcomes, *n* (%)						
Hypoalbuminemia on Day 1	58 (71.6)	67 (56.3)	0.028	48 (64.0)	77 (61.6)	0.734
Mortality	29 (35.8)	19 (16.0)	0.001	27 (36.0)	21 (16.8)	**0.002**

[a]Independent t-test for albumin, Chi-square test for categorical outcomes. Values below 0.05 are highlighted. Bold values indicate *P*<0.05.

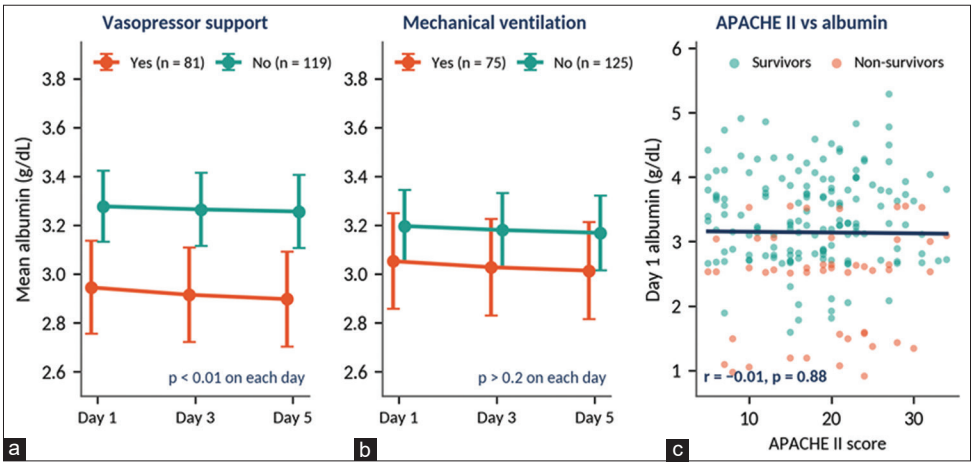


Figure 10: Albumin, organ support and illness severity. (a and b) Mean serum albumin (with 95% confidence intervals) on Day 1, Day 3, and Day 5 in patients with and without vasopressor support (a) or mechanical ventilation (b). (c) Day 1 albumin against APACHE II score; the line is the linear fit and r is Pearson's correlation coefficient. APACHE II: Acute Physiology and Chronic Health Evaluation II

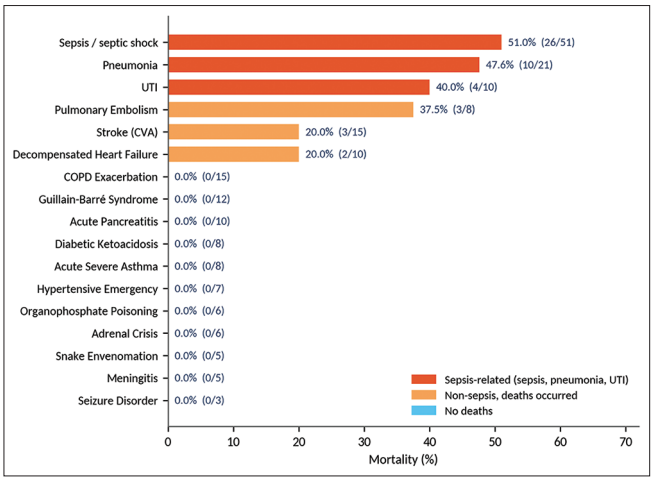


Figure 11: Mortality by primary diagnosis. Bars show mortality (%) with deaths/patients in parentheses; sepsis-related diagnoses (sepsis, pneumonia, and urinary tract infection) are shown in red, other diagnoses with deaths in orange and diagnoses without deaths in blue. UTI: Urinary tract infection

Comparison with Previous Studies

The link between hypoalbuminemia and mortality is well established. A meta-analysis of cohort studies found that lower albumin was associated with mortality and morbidity in a dose-dependent manner,[8] and large database analyses, single-center cohorts, and recent reviews have confirmed this in general ICU populations and in sepsis.[10-13,22] In septic shock, an admission albumin cut-off of 2.45 g/dL predicted short- and long-term mortality in more than a thousand patients,[23] which is close to our severe category (<2.5 g/dL), and in a prospective sepsis cohort, hypoalbuminemia was associated with a markedly higher 28-day mortality and an albumin discriminative ability comparable with the APACHE II score.[18] Albumin has likewise been linked to 30-day mortality in infected patients presenting to the emergency department,[24,25] and to mortality in patients receiving renal replacement therapy.[26,27]

Our findings on serial measurements agree with earlier work showing that albumin trajectories carry prognostic information.[14,15] In the closest comparator, a study with the same design, admission albumin did not differ significantly between survivors and non-survivors (3.30 vs. 3.42 g/dL), whereas the difference emerged on Day 3 and Day 5, and albumin fell significantly from Day 1 in non-survivors.[16] In contrast, our non-survivors already had markedly lower albumin at admission (2.38 ± 0.82 vs. 3.38 ± 0.71 g/dL), which may reflect the high proportion of sepsis-related illness among our deaths (83.3%) and possibly the referral of sicker patients to a tertiary center. Nevertheless, the fall from Day 1 to Day 5 was again larger in non-survivors (−0.09 vs. −0.01 g/dL).

Possible Mechanisms

Albumin concentration in critical illness is determined by reduced hepatic synthesis during the acute-phase response, increased capillary leak, dilution, and catabolism.[7,8,28] Lower albumin in turn implies reduced oncotic pressure, weaker antioxidant

Table 8: Serum albumin and mortality across APACHE II, ICU-stay, and socio-economic strata

Stratum	*Patients, n*	*Day 1 albumin, g/dL*	*Day 5 albumin, g/dL*	*Mortality, n (%)*
APACHE II category				
Low risk (<15)	59	3.20±0.86	3.17±0.89	13 (22.0)
Moderate risk (15–24)	102	3.09±0.85	3.07±0.87	22 (21.6)
High risk (>24)	39	3.19±0.86	3.14±0.88	13 (33.3)
P-value[a]		0.688	0.761	0.314
Length of ICU stay				
<7 days	143	3.14±0.85	3.11±0.87	36 (25.2)
7–14 days	42	3.03±0.87	2.99±0.90	7 (16.7)
>14 days	15	3.51±0.79	3.45±0.82	5 (33.3)
P-value[a]		0.175	0.215	0.356
Socio-economic status				
Upper class	18	3.06±1.04	3.05±1.06	3 (16.7)
Middle class	110	3.09±0.83	3.06±0.86	31 (28.2)
Lower class	72	3.24±0.84	3.21±0.86	14 (19.4)
P-value[a]		0.489	0.493	0.301
Correlation of APACHE II score with albumin				
Day 1 albumin	200	r=−0.011	ρ=−0.014	*P*=0.88
Day 5 albumin	200	r=−0.019	ρ=−0.021	*P*=0.79

Albumin values are mean±SD. [a]One-way analysis of variance for albumin, Chi-square test for mortality. r: Pearson's correlation coefficient; ρ: Spearman's correlation coefficient, APACHE II: Acute physiology and chronic health evaluation II, ICU: Intensive care unit

Table 9: Serial serum albumin (g/dL) in survivors and non-survivors by primary diagnosis

Primary diagnosis	*Outcome*	*n*	*Day 1*	*Day 3*	*Day 5*	*Change, Day 1–Day 5*
Sepsis-related diagnoses						
Sepsis/septic shock	Survivors	25	3.20±0.70	3.20±0.70	3.18±0.71	−0.02
	Non-survivors	26	2.34±0.87	2.27±0.88	2.26±0.90	−0.08
Pneumonia	Survivors	11	3.46±1.07	3.46±1.06	3.47±1.04	+0.02
	Non-survivors	10	2.60±0.66	2.52±0.66	2.48±0.67	−0.12
Urinary tract infection	Survivors	6	3.21±0.53	3.21±0.54	3.22±0.54	+0.01
	Non-survivors	4	2.04±0.92	2.01±0.98	1.98±1.00	−0.06
Non-sepsis diagnoses						
Stroke	Survivors	12	3.37±0.65	3.38±0.63	3.38±0.62	+0.02
	Non-survivors	3	2.42±1.18	2.32±1.17	2.26±1.18	−0.16
Decompensated heart failure	Survivors	8	3.10±0.64	3.09±0.65	3.08±0.67	−0.02
	Non-survivors	2	2.04±0.68	2.00±0.66	1.95±0.65	−0.09
Pulmonary embolism	Survivors	5	3.42±0.56	3.39±0.57	3.37±0.56	−0.05
	Non-survivors	3	2.58±0.98	2.55±0.97	2.54±1.02	−0.04

Values are mean±SD; change is Day 5 minus Day 1 (mean). No hypothesis tests were performed because of small subgroup sizes

and endotoxin-binding capacity,[5,6] and a higher free fraction of albumin-bound drugs,[29] all of which may aggravate organ dysfunction. The greater vasopressor requirement in our patients with lower albumin fits this pathway, although vasopressor dependence is itself a marker of severity and the association may be bidirectional.

Albumin and Disease Severity Scores

Albumin did not correlate with APACHE II score in this cohort, and APACHE II category was not significantly related to mortality. This suggests that in our setting, albumin captured prognostic information that was not tracked by the APACHE II score, possibly because most deaths were concentrated in infectious diagnoses and albumin partly reflects infection-related inflammation. The combination of albumin with SOFA has been reported to improve mortality stratification in septic shock,[17] and this deserves testing against APACHE II in larger Indian cohorts. Interestingly, non-survivors were less likely to have pre-existing diabetes or hypertension, possibly because deaths clustered in previously healthy patients with acute infection; this finding should be interpreted cautiously.

Clinical Implications

Serum albumin is inexpensive, widely available, and reproducible. A low admission value, and particularly a value below 2.5 g/dL or a downward trend, could flag patients who merit closer monitoring and earlier escalation of care. Albumin should be interpreted as a prognostic indicator alongside clinical assessment rather than as a therapeutic target, because it is influenced by fluids, liver and renal function, and inflammation, and because benefit from albumin replacement in this setting remains uncertain.[8,10]

Strengths and Limitations

Strengths include the prospective design, consecutive enrolment, uniform laboratory methodology, and a mixed medical ICU population. Limitations should be acknowledged. First, this was a single-center study with a modest number of deaths (n = 48), so estimates for mild hypoalbuminemia and for diagnosis-specific subgroups are imprecise. Second, analyses were unadjusted; a multivariable model including age, severity, and diagnosis was not performed, so albumin cannot be called an independent predictor, and sepsis-related diagnoses accounted for most deaths. Third, patients who died within 3 days were excluded, which may

under-represent the most severely ill patients. Fourth, intravenous fluids, transfusions, albumin infusions, and nutritional support were not controlled for, and inflammatory markers such as C-reactive protein and procalcitonin were not measured. Fifth, receiver operating characteristic analysis was not performed and no direct comparison was made between serial and single measurements, so the added value of serial sampling over admission albumin remains to be shown. Sixth, the trend categories were qualitative and their operational thresholds should be standardized in future work, and the mean fall in albumin over 5 days was small in absolute terms. Finally, only APACHE II was used to grade severity and follow-up ended at discharge or death.

200 Critically ill adults	**24.0%** Mortality (48/200)	**62.5%** Hypoalbuminemia on admission	**RR 6.43** Albumin <2.5 versus ≥3.5 g/dL	**OR 5.87** Deteriorating versus improving trend

Key Points

- Albumin was already markedly lower on admission in non-survivors, and the gap persisted through Day 5
- Mortality increased stepwise with the severity of hypoalbuminemia, from 9.3% to 60.0%
- A deteriorating albumin trend was linked to a nearly six-fold higher odds of death than an improving trend.

Conclusion

In critically ill adults, low admission serum albumin and a deteriorating albumin trend over the first 5 days were associated with substantially higher mortality, with a clear dose–response relationship across the degree of hypoalbuminemia. Serial albumin estimation is simple and low-cost and may help identify high-risk patients early, particularly where advanced biomarkers are unavailable. Larger multicenter studies with multivariable adjustment, receiver operating characteristic analysis, and comparison with a single admission measurement are needed before it can be recommended as an independent prognostic tool.

Ethics approval and consent

Approved by the Institutional Ethics Committee of L.N. Medical College and Research Center, Bhopal; written informed consent was obtained from all participants or their legal guardians.

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