The Combined Use of Interleukin-6 with Serum Albumin for Mortality Prediction in Critically Ill Elderly Patients: The Interleukin-6-to-albumin Ratio

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ABSTRACT

Background: The association between interleukin-6 (IL-6) and serum albumin (ALB) with mortality in critically ill elderly patients, either as stand-alone biomarkers or in combination, has been scarcely reported. We, therefore, aimed to investigate the prognostic value of the IL-6-to-albumin ratio in this special population.

Patients and methods: This was a cross-sectional study conducted in the mixed intensive care unit (ICU) of two university-affiliated hospitals in Malaysia. Consecutive elderly patients (aged above or equal to 60 years) admitted to the ICU, who underwent simultaneous measurement of plasma IL-6 and serum ALB, were recruited. The prognostic value of the IL-6-to-albumin ratio was assessed by analysis of the receiver-operating characteristic (ROC) curve.

Results: A total of 112 critically ill elderly patients were recruited. The outcome of all-cause ICU mortality was 22.3%. The calculated IL-6-to-albumin ratio was significantly higher in the non-survivors compared to the survivors {14.1 [interquartile range (IQR), 6.5–26.7] vs 2.5 [(IQR, 0.6–9.2) pg/mL, $p <0.001$]}. The area under the curve (AUC) of IL-6-to-albumin ratio for discrimination of ICU mortality was 0.766 [95% confidence interval (CI), 0.667–0.865, $p <0.001$] which was slightly higher than that of IL-6 and albumin alone. The ideal cut-off value of the IL-6-to-albumin ratio was above 5.7 with a sensitivity of 80.0% and specificity of 64.4%. After adjusting for severity of illness, the IL-6-to-albumin ratio remained as an independent predictor of ICU mortality with an adjusted odd ratio of 0.975 (95% CI, 0.952–0.999, $p = 0.039$).

Conclusion: The IL-6-to-albumin ratio offers a slight improvement in mortality prediction than either of its constituent individual biomarkers and as such, it may be a potential tool to aid in the prognostication of critically ill elderly patients although this requires further validation in a larger prospective study.

Keywords: Albumin, Elderly, Intensive care unit, Intensive care unit mortality, Interleukin-6.

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INTRODUCTION

The global population of elderly patients has increased substantially in the recent years.[1] This leads to an increase in the demand for healthcare services of the elderly patients, including for the ICU treatment.[2] Following ICU admission, elderly patients are more likely than younger patients to experience adverse outcomes, including mortality.[3,4] The healthcare-related cost in elderly ICU patients is also significantly higher than that in younger ICU patients.[5] Prognostication is therefore important to help the ICU physicians to determine the direction and intensity of treatment for this special population while balancing with judicious utilization of the limited and high-cost resources.

The traditional method to prognosticate critically ill patients is to use the risk prediction models, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score. However, such models were constructed for general use in heterogeneous ICU populations and have only been validated in a few small studies of elderly patients.[6–8] Prognostication of critically ill patients may be refined by the use of biomarkers of certain pathophysiologic processes that are not necessarily reflected by established clinical risk factors. Examples of such biomarkers are IL-6 and serum ALB. The IL-6 is both a

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pro- and anti-inflammatory cytokine that has been evaluated in multiple studies in the critical care setting. Authors have suggested that IL-6 can be used as a prognostic tool in adult patients with critical illness, sepsis, and unstable coronary artery disease.[9–11] On the other hand, serum ALB is a negative acute-phase protein; the presence of hypoalbuminemia has been associated with ICU mortality in critically ill adult patients.[12] Notably, an increase in serum IL-6 and a decrease in serum ALB levels are also seen in aging.[13,14] These derangements can be enhanced with a critical illness.

Emerging evidence suggests that serum cytokine values, such as IL-6, when used in combination with serum ALB, may enhance its predictive capacity.[15] This is probably because the IL-6-to-albumin ratio incorporates deviations of these parameters into a single direction during illness in critically ill patients. To our knowledge, the clinical association of the IL-6-to-albumin ratio with mortality in the elderly subgroup of critically ill patients has not been investigated so far. This is the reason why we aimed to investigate the prognostic value of the IL-6-to-albumin ratio in this special population treated at our institution that we present in this study.

PATIENTS AND METHODS

Study Design

This was a cross-sectional study conducted in the ICU of two university-affiliated hospitals in Malaysia. The protocol of the study was approved by the human research ethics committee of respective institutions (Codes: USM/JEPEM/21010046 and IREC 2021-009). The recruitment was conducted over a 5-month period from 28 October 2021 to 28 March 2022. The first institution is comprised of a 9-bed medical ICU and a 5-bed surgical ICU while the other institution has 22 functioning beds in its mixed ICU.

Study Participants

All consecutive elderly patients who were admitted to the two participating ICU during the study period were assessed for eligibility. We followed the definition by the United Nation that an elderly is defined as a person who is over 60 years of age.[16] Patients who had their length of stay below 24 hours in the ICU or were transferred from another ICU were excluded. Patients could only participate once in this research; for those who had more than one admission to ICU, only the first episode was analyzed. After screening, eligible patients or their legally acceptable representatives were approached for written informed consent.

Study Procedure

In consented patients, their baseline data were collected within the first 24 hours of the ICU admission. Data collected were as follows: Age, gender, body mass index, admission category, baseline comorbidity as assessed by Charlson comorbidity index, baseline severity of illness as assessed by APACHE II score, baseline organ dysfunction as assessed by SOFA score, baseline nutritional status as assessed by Nutrition Risk in Critically ill (NUTRIC) score, frailty index assessment by clinical frailty scale, treatment received in the first 24 hours of ICU admission in terms of mechanical ventilation, inotropic or vasopressor support, and renal replacement therapy, and serum ALB level. After the baseline data collection, 2 mL of whole blood were sampled from the arterial line of each patient into the ethylene diamine tetra acetic acid bottle. The samples were immediately centrifuged under 3,600 rotations per minute for 10

minutes to obtain the plasma for IL-6 measurement. All patients were followed up until ICU discharge to determine their outcome, "all-cause ICU mortality."

Interleukin-6 and Albumin Measurements

Interleukin-6 was measured by point-of-care analyzers [FinecareTM IL-6 Rapid Quantitative test (CIGA Healthcare Ltd., Ballymena, UK)] which were available in the two participating ICUs. The measurement is based on fluorescence immunoassay technology, which uses a sandwich immunodetection method to measure the plasma level of IL-6 quantitatively. The assay has a measuring range of 3–4,000 pg/mL. The manufacturer-claimed intra-assay and interassay coefficient of variations are less than 15%. The IL-6 results were available after 15 min and all measurements were performed by a properly trained research assistant in each participating ICU. Serum albumin was measured in the central laboratory of each center as part of the routine investigations in the ICU. The reference range of serum ALB in our laboratories is 35–45 gm/L. The IL-6-to-albumin ratio was calculated by dividing plasma IL-6 by serum ALB.

Statistical Analysis

The statistical analysis in this study was performed using SPSS, v.26 (IBM software) and MedCalc®, v.20.023. Patients' baseline characteristics were reported as mean standard deviation (SD) or median (IQR) for continuous variables and counts (%) for categorial variables. Normality of distribution of the continuous variables was tested with the Shapiro–Wilk test. The patients were classified into two groups as follows: The ICU survivors or the non-survivors. The difference in the baseline characteristics between the two groups was compared with an independent t-test or Mann–Whitney U test for continuous variables, depending on the normality of distribution. For categorical variables, the Chi-squared test was used. All tests were two-sided and $p < 0.05$ was considered as statistically significant.

To determine the predictive performance for the IL-6-to-albumin ratio, we first compared its value between the two groups using an independent t-test or Mann–Whitney U test, if it deviates from normality of distribution. If this was significant, we proceeded to construct the ROC curve to determine the AUC, ideal cut-off point, sensitivity, and specificity of each biomarker. Finally, we performed a multivariate logistic regression analysis, adjusting for potential confounders, to determine whether the IL-6-to-albumin ratio was an independent predictor of ICU mortality. This was expressed as an adjusted odds ratio (OR) with a 95% CI.
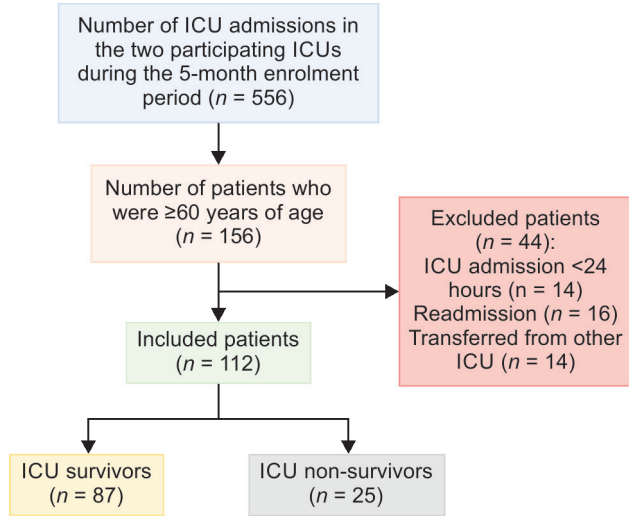
Sample-size Calculation

In this study, we wanted to show that the AUC of 0.7 for IL-6 was significantly different from the null hypothesis value of 0.5. Using the ratio of the sample in negative to positive groups of 3:1,[17] significance at 0.05 and power of 0.8, we needed to study 66 ICU survivors and 22 ICU non-survivors, giving a total of at least 88 critically ill elderly patients to be studied.

RESULTS

Baseline Demographic and Clinical Characteristics

Throughout the 5-month recruitment period, there was a total of 556 ICU admissions (Flowchart 1). Among these, 156 (28.1%) were elderly patients; 44 (28.2%) of the elderly patients did not fulfil the study criteria and were thus excluded from the study. Of note,

Flowchart 1: Schematic flowchart of the selection process of eligible patients

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Number of ICU admissions in
the two participating ICUs
during the 5-month enrolment
period (n = 556)
        │
        ▼
Number of patients who
were ≥60 years of age          Excluded patients
(n = 156)          ──────▶      (n = 44):
        │                       ICU admission <24
        │                       hours (n = 14)
        │                       Readmission (n = 16)
        ▼                       Transferred from other
Included patients               ICU (n = 14)
(n = 112)
        │
   ┌────┴────┐
   ▼         ▼
ICU survivors   ICU non-survivors
(n = 87)        (n = 25)
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Table 1: Baseline demographic and clinical characteristics

|	ICU survivors (n = 87)	ICU non-survivors (n = 25)	p-value
Demographic			
Age (years)	68 (7)	69 (6)	0.455
Sex			0.779
Male	48 (55.2)	13 (52.0)	
Female	39 (44.8)	12 (48.0)	
BMI (kg/m^2)	24.3 (4.0)	25.7 (4.9)	0.204
Clinical			
Category of admission			0.721
Medical	59 (67.8)	16 (64.0)	
Surgical	17 (32.2)	3 (36.0)	
Primary diagnosis			0.118
Cardiovascular	12 (13.8)	3 (12.0)	
Pulmonary	18 (20.7)	8 (32.0)	
Infectious	21 (24.1)	3 (12.0)	
Gastrointestinal	7 (8.0)	3 (12.0)	
Neurological	4 (4.6)	1 (4.0)	
Trauma	2 (2.3)	0	
Post-elective	14 (16.1)	0	
Post-emergency	8 (9.2)	7 (28.0)	
Others	1 (1.1)	0	
Pre-ICU status			
Charlson comorbidity index	5.0 (1.7)	4.9 (1.8)	0.807
Clinical frailty scale	5.5 (1.5)	5.6 (1.6)	0.632
Severity of illness			
APACHE II score	13.6 (6.5)	18.2 (6.3)	<0.001
SOFA score	5.1 (3.0)	7.8 (3.1)	<0.001
Nutritional status			
NUTRIC score	3.6 (1.4)	5.4 (1.5)	<0.001
Treatment received in the first 24 hours in ICU			
Mechanical ventilation	41 (47.1)	22 (88.0)	<0.001
Inotropes or vasopressors	40 (46.0)	23 (92.0)	<0.001
Renal replacement therapy	18 (20.7)	7 (28.0)	0.439

APACHE II, Acute Physiological Assessment and Chronic Health Evaluation II; NUTRIC, Nutrition Risk in Critically ill; SOFA, Sequential Organ Failure Assessment

the outcome of ICU mortality was reached in 25 (22.3%) of the 112 included elderly patients.

The baseline demographic and clinical characteristics of the included elderly patients are illustrated in Table 1. There was no statistically significant difference between the two groups except that the ICU non-survivors had higher means of APACHE II score [18.2 (SD = 6.3) vs 13.6 (SD = 6.5), p <0.001], SOFA score [7.8 (SD = 3.1) vs 5.1 (SD = 3.0) p <0.001] and NUTRIC score [5.4 (SD = 1.5) vs 3.6 (SD = 1.4), p <0.001] compared to the ICU survivors. Also, a significantly higher proportion of the ICU non-survivors compared to the ICU survivors received mechanical ventilation (88.0% vs 47.1%, p <0.001) and inotropes or vasopressors (92.0% vs 46.0%, p <0.001) during the first 24 hours of ICU admission.

Predictive Performance of the Biomarkers

Baseline plasma level of IL-6 was found to be significantly higher [372.7 (IQR, 124.3–624.9) vs 80.2 (IQR 21.2–270.8) pg/mL, p = 0.002] and serum level of albumin was found to be significantly lower [24.0 (IQR, 19.5–20.0) vs 30.0 (IQR 25.0–34.0) gm/L, p <0.001] in the ICU non-survivors compared to the ICU survivors. Understandably, the calculated ratio of IL-6-to-albumin was significantly higher in the ICU non-survivors compared to the ICU survivors [14.1 (IQR, 6.5–26.0) vs 2.5 (IQR, 0.6–9.2), p <0.001].

In a ROC curve analysis, the discriminative abilities of both serum ALB and plasma IL-6 for ICU mortality were clinically valid as indicated by their AUC of 0.703 (Fig. 1A) and 0.753 (Fig. 1B), respectively. Of note, the ratio of IL-6-to-albumin was slightly superior to its constituent individual biomarkers in discriminating the ICU survivors from the non-survivors, with an AUC of 0.766 (95% CI, 0.667–0.865, p <0.001) (Fig. 1C). The ideal cut-off point of the ratio was above 5.71. At this cut-off point, the sensitivity was 80.0% and specificity was 64.4%.

Additionally, the correlation between serum ALB and plasma IL-6 is depicted in Figure 2 which had a significant but weak negative correlation as indicated by a correlation coefficient of −0.283 (p = 0.003).

Independent Value of IL-6-to-albumin Ratio

In a multivariable logistic regression analysis, after adjusting for the APACHE II score and SOFA score, the IL-6-to-albumin ratio remained as an independent predictor of ICU mortality in our critically ill elderly patients, with an adjusted OR of 0.975 (95% CI, 0.952-0.999, p = 0.039) (Table 2). SOFA score was also found to be an independent predictor of ICU mortality, with an adjusted OR of 0.812 (95% CI, 0.679-0.972, p = 0.023), but not the APACHE II score. The overall model fit had a Nagelkerke R^2-value of 0.2741. The Hosmer–Lemeshow goodness of fit test revealed a Chi-squared value of 8.692 (p = 0.369), indicating a good fit to the data.

DISCUSSION

In this prospective cohort study of 112 critically ill elderly patients, we found that serum ALB and plasma IL-6 measured on ICU admission had significant associations with ICU mortality. Both biomarkers were clinically valid to discriminate critically ill elderly patients who went on to die or survive the ICU stay. Of note, when the IL-6 was used in combination with albumin, the IL-6-to-albumin ratio had a slightly superior predictive performance than either
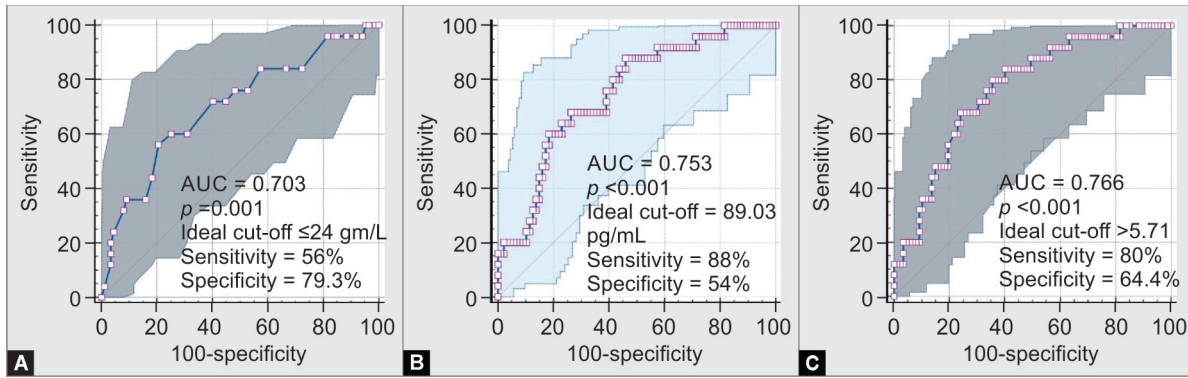
Figs 1A to C: The ROC curve analysis for (A) albumin; (B) IL-6; and (C) IL-6-to-albumin ratio for ICU mortality
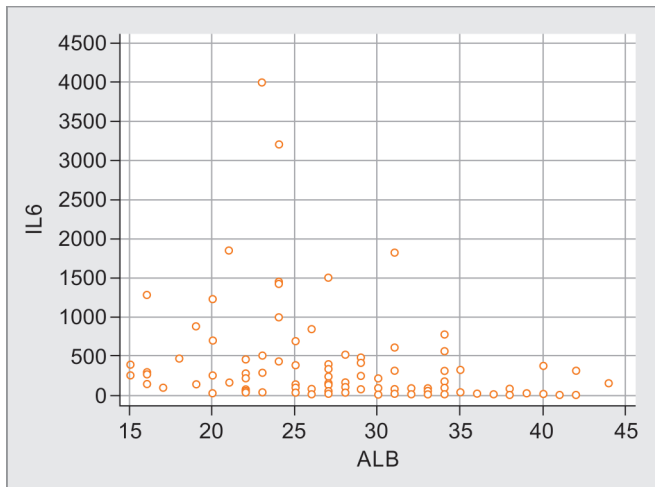

Fig. 2: A scatter diagram of correlation between serum albumin (ALB) on the x-axis and plasma IL-6 on the y-axis

Table 2: The odd ratio of IL-6-to-albumin-ratio adjusted for APACHE II score and SOFA score

Variables	Odd ratio	95% CI	p-value
IL-6-to-albumin-ratio	0.975	0.952–0.999	0.039
APACHE II score	0.962	0.885–1.045	0.357
SOFA score	0.812	0.679–0.972	0.023

biomarker used alone. After adjusting for potential confounders of the severity of illness by APACHE II score and organ dysfunction by SOFA score, the IL-6-to-albumin ratio remained as an independent predictor of ICU mortality in our critically ill elderly cohort.

Predicting the outcome of elderly patients who are admitted to ICU can be difficult with the traditional method using risk prediction models, as these were constructed for general use in heterogeneous ICU populations. Biomarkers of certain pathophysiologic processes may have value to aid prognostication of the critically ill elderly patients. For example, serum ALB, a routinely measured biomarker in the ICU, represents the aging process as well as inflammation and malnutrition,[18] of which are all common in the elderly critically ill patients. However, routinely measured laboratory parameters display limited accuracy in predicting mortality, as with serum ALB. On the other hand, the role of IL-6 in aging and age-related conditions such as frailty is now clearly established.[19] However, this has not been well studied in the critically ill elderly cohort. In the current study, we have

shown that a combination of albumin and IL-6, in the form of an IL-6-to-albumin ratio, may be a slightly better tool to aid mortality prediction in this special population than its individual constituent biomarkers, probably because it reflects wider pathophysiologic processes involved in aging and critical illness.

Our results are novel with respect to the combined use of IL-6 and serum ALB for mortality prediction in critically ill elderly patients. A few previous studies have attempted a similar strategy of combining cytokine values with serum ALB, albeit in different conditions, with promising results. For example, a recent study conducted on COVID-19 patients demonstrated that the combined ratio of IL-15-to-albumin improved the early recognition of patients with an increased risk of death.[15] In line with previous evidence, we now report that combining IL-6 with albumin in a single prognostic ratio slightly improved our ability to identify critically ill elderly patients who are at high risk of ICU mortality. More importantly, we believe that we have added new knowledge to the critical care literature since data regarding the elderly patients being admitted to the ICU mainly come from high-income countries. Also, biomarker data from the current literature are scarce in this special population,[20] since such studies usually exclude elderly patients, due to age-based exclusion criteria.

Although our results are encouraging, this study has several pertinent limitations. The prognostic performance of the IL-6-to-albumin ratio in this study predicted our dual-centered data set, but whether it is generalizable to external populations is unknown. While we have attempted to control for confounding factors by modeling the IL-6-to-albumin ratio in a logistic regression model, we may have failed to account for other unmeasured confounders or collinear effects. In addition, the measurement of IL-6 plasma levels may not be widely available, thus limiting its value in daily clinical practice. However, the IL-6 in this study is measured with a point-of-care device, which is considerably practical if it is to be applied in daily clinical practice.

CONCLUSION

The combined use of IL-6 with serum ALB in the form of IL-6-to-albumin ratio independently predicted ICU mortality with slightly better performance than its constituent individual biomarkers in our critically ill elderly cohort. Further larger multicenter prospective studies are warranted to validate our current findings and to assess whether the IL-6-to-albumin ratio may be successfully integrated with physicians' clinical practice to improve the prediction of mortality and clinical decision-making at the bedside of critically ill elderly patients.

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