ORIGINAL RESEARCH

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PERCENTAGE CHANGES IN ALBUMIN LEVEL DURING FIRST WEEK OF ADMISSION AS A PREDICTOR OF 28-DAY MORTALITY IN CRITICALLY ILL PATIENTS WHO ARE TAKING INTRAVENOUS HUMAN ALBUMIN

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ABSTRACT:

Objectives: Decreasing in albumin levels are widely used to predict mortality. We evaluate the overall 28-day mortality prognostic value of percentage changes in albumin levels during first week of admission (%Δ ALB_{1wk}) in comparison to either albumin level at admission (ALB_1) or albumin level after 1 week of admission (ALB_2) taking into consideration the instability of critically ill patients.

Methods: We retrospectively obtained serial measurements of albumin levels of patients admitted to our adult Intensive Care Unit (ICU) between April 2017 and Sep 2018. Patients will be excluded if they discharged or died before 1 week of ICU admission. A receiver operating characteristic (ROC) analysis was conducted to compare the prognostic efficacy of the three tested prognosticators.

Results: A total of 163 critically ill patients were finally included in this study. The mean age was 58.37±9.96 years, and 112 (68.71%) were male. The overall 28-day ICU mortality rate was 39.26% (64 patients). The %Δ ALB_{1wk} was significantly higher in nonsurvivors than in survivors (-11.47%±8.23% vs 0.69%±4.61%; P<0.05). The prognostic value of the % ΔALB_{1wk} (0.929) was significantly greater than that of ALB_1 and ALB_2(0.266and 0.655, respectively; P<0.001).

Conclusion In comparison to Alb_1, the %ΔALB_{1wk} and Alb_2have a significantly prognostication which is significantly higher in % ΔALB_{1wk} than ALB_2 with a sensitivity and performance of (93.94% and 75.19% vs 59.59% and 29.91%, respectively; P<0.001). The % Δ ALB_{1wk} may serve a novel independent prognosticating indicator for critically ill patient's mortality who are taking intravenous human albumin.

KEY WORDS: Hypoalbuminemia, Critical, Mortality, Changes.

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INTRODUCTION

Mortality is the worst clinical outcome in ICU setting. Early prediction of mortality in critically ill patients can help to stratified patients and promptly give the best treatment. Therefore, predicting mortality risk is a major priority of ICU care. Several prognostic indices have been suggested to predict the risk of critically ill patient's mortality, but some predictive indices are too complicated to calculate the mortality probability. As a result, there has been an increasing need to establish simplified clinical mortality indicators while maintaining the prognostic accuracy and performance of the prognosticator. Decreasing in albumin levels are associated with poor outcomes in critically ill patients and are widely used to predict mortality[1]. The prognostic roles of hypoalbuminemia can be explained by their negative phase reactant in acute and chronic inflammatory[2-4],and the prevalence of malnutrition status in critically ill patients[5, 6], respectively. However, many studies have recently investigated whether the ALB_1, ALB_2, or %Δ ALB an effectively reflect the prognosis of critically ill patients, few studies have ever attempted examining the mortality prognostic value of these prognosticators in critical ill patients who are taking intravenous human albumin. Based on these properties, we speculated that the serial measurements of albumin levels could be used as a predictive marker for mortality and we investigated the use of the %Δ ALB_{1wk} as an independent predictor of overall 28-day ICU mortalitytaking into consideration the instability and dynamic changes of these critically ill patients. It also aimed to determine the optimal cut-off point and the mortality prognosticator performance of the significant prognostic indicators. We hypothesized that this percentage changes could be used a surrogate independent predictor and a novel prognosticator for critically ill patient's mortality.

METHODS AND SUBJECTS

Study design and setting

This was a single-center retrospective study conducted in the department of adult ICU of King Hussein Medical Center (KHMC) at Royal Medical Services in Jordan. This study was approved by our institutional review board, and a requirement for consent was waived owing to its retrospective design. This study included a cohort of critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem between April 2017 and Sep 2018 and at least their baseline demographic data, baseline anthropometric data, ALB_1, ALB_2, average total calories administered (TC_{avg}), number of co-morbidities, primary cause of admission, pre-ICU admission days, ICU admission days, lab results to calculate Child-Pugh score, and average administered volume of Human Albumin® 20% were known. Patients were excluded if they discharged or died before 1 week of ICU admission.

Data collection

Demographics and clinical data were collected from electronic medical records. Laboratory parameters such as albumin were obtained when admitted to the ICU and 1 week after as part of the routine testing.The primary outcome was overall 28-day ICU mortality. Survival to ICU discharge was defined as discharge from the ICU alive or dead.

Statistical analysis

All patient's variables were compared using the Mann-Whitney U test and the independent samples t test for the continuous variables, and the χ^2 test for categorical variables. Continuous variables were expressed as means ± standard deviation and categorical variables as numbers with percentages or medians (interquartile ranges) for the description of all variables. Univariate analysiswas conducted first for most possible affected patient's variables associated with ICU mortality followed by multivariate logistic regression analysis and values were compared for the two tested groups (survivors vs nonsurvivors). To determine the best cutoff values for the three tested prognosticators a receiver operating characteristic (ROC) curve was generated and youden's index was calculated; sensitivities, specificities, positive and negative predictive values, and accuracy index were also calculated. We determined predictive performance using ROC curves with logistic regression models to compare and assess for equality of the area under the curve (AUC) using the DeLong test. Statisticalanalyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

A total of 913 critically ill patients were admitted to our ICU during the study period. Of those, 750 patients were excluded because they either discharged or died before 1 week of ICU admission (n=388) or the critically ill patient's data can't be obtained or incomplete (n=362). The remaining 163critically ill patients were finally included in this study. The mean age was 58.37±9.96 years, and 112 subjects (68.71%) were male. The overall 28-day ICU mortality rate was 39.26% (64 patients). Demographics/Admission co-morbidities and

diagnostics/Anthropometrics, and baseline/follow-up data of the study's critically ill patients are shown in Table 1 and Table 2, respectively. ALB_1 was significantly higher in nonsurvivors than in survivors (2.94±0.39 vs 2.63±0.20, respectively; P<0.05) in contrast to ALB_2 which was significantly higher in survivors than in nonsurvivors (2.64±0.12 vs 2.57±0.13, respectively; P<0.05).

Table 1. Demographics/Admission co-morbidities and diagnostics/Anthropometrics comparison of study'sICU patients.

Variables		Total (n=163)	Survivors (n=99)	Nonsurvivors (n=64)	P-Value
Age (Yrs)		58.37±9.96	58.55±9.948	58.09±10.053	0.917 (NS)
Gender	Male	112 (68.71%)	67 (67.68%)	45 (70.31%)	0.796 (NS)
	Female	51 (31.29%)	32 (32.32%)	19 (29.69%)	
Day(s) Pre-ICU admission (day(s))		4.27±3.91	2.23±1.06	7.42±4.57	0.000 (S)
ICU Stay day(s)		12.40±4.79	9.23±1.06	17.30±4.14	0.000 (S)
Hospital Stay day(s)		16.67±6.81	11.46±2.12	24.72±1.98	0.003 (S)
Number of comorbidities	0, 1	74 (45.39%)	52 (52.53%)	22 (34.38%)	0.061 (NS)
	2 , 3, 4+	89 (54.60%))	47 (47.47%)	42 (65.63%)	
Admission class	Medical	105 (64.42%)	50 (50.51%)	55 (85.94%)	0.002 (S)
	Surgical	58 (35.58%)	49 (49.49%)	9 (14.06%)	
Primary admission diagnosis	Cardiovascular/Vascular	26 (15.95%)	17 (17.17%)	9 (14.06%)	0.019 (S)
	Multiple Trauma	18 (11.04%)	8 (8.08%)	10 (15.63%)	
	Neurological	24 (14.72%)	19 (19.19%)	5 (7.81%)	
	Respiratory	45 (27.61%)	36 (36.36%)	9 (14.06%)	
	Sepsis	31 (19.02%)	12 (12.12%)	19 (29.69%)	
	Gastrointestinal	8 (4.91%)	4 (4.04%)	4 (6.25%)	
	Renal	9 (5.52%)	2 (2.02%)	7 (10.94%)	
	Others	2 (1.23%)	1 (1.01%)	1 (1.58%)	
BW_1 (Kg)		74.17±10.24	74.63±10.06	73.45±10.56	0.609 (NS)
IBW_1 (Kg)		64.97±6.90	64.60±6.77	65.56±7.12	0.813 (NS)
$AdjBW_1$ (Kg)		68.65±6.16	68.61±6.18	68.72±6.18	0.908 (NS)
BMI_1 (Kg/m²)		25.92±4.00	26.19±3.85	25.50±4.22	0.311 (NS)
28-day ICU Survival		99 (60.74%)			
28-day ICU Mortality	Overall Mortality	64 (39.26%)			
	Early Mortality (≤14 days)	16 (9.82%)			
	Late Mortality (>14 days)	48 (29.45%)			

Values are presented as mean±standard deviation or number (%).
ICU: Intensive care unit.
S: Significant (P-Value <0.05).
NS: Nonsignificant (P-Value >0.05).
BW: Body weight.
IBW: Ideal body weight.
AdjBW: Adjusted body weight.
1: Baseline after ICU admission.
2: 1 week after ICU admission.
BMI: Body mass index.

Table 2. Baseline and follow-up data comparison of study's critically ill patients.

Variables		Total (n=163)	Survivors (n=99)	Nonsurvivors (n=64)	P-Value
Norepinephrine Rate $_{avg}$ (mcg/min)		9.53±1.79	9.27±1.68	9.94±1.89	0.724 (NS)
GCS_{avg} (3-15)		12 (12-13)	12 (12-13)	12 (12-13)	0.341 (NS)
GCS $_{avg}$ (3-15)	Fully responsive (15)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.081 (NS)
	Partially responsive (9-14)	163 (100%)	99 (100%)	64 (100%)	
	Comatose (4-8)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
	Totally unresponsive (3)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Child-Pugh Score (5-15)		6 (6-8)	6 (6-8)	6 (6-7)	0.088 (NS)
Liver severity$_1$	Normal/At Risk (5-6)	124 (76.07%)	70 (70.71%)	54 (84.38%)	0.065 (NS)
	Moderate (7-9)	38 (23.93%)	28 (28.28%)	10 (15.63%)	
	Severe (10-15)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
ALB_1 (g/dl)		2.75±0.32	2.63±0.20	2.94±0.39	0.00 (S)
Human Albumin Dose $_{avg}$ (g/day)		16.99±5.11	18.89±3.16	14.06±6.09	0.000 (S)
ALB_2 (g/dl)		2.61±0.13	2.64±0.12	2.57±0.13	0.442 (NS)
% Δ ALB_{1wk} (%)		-4.08%±8.65%	0.69%±4.61%	-11.47%±8.23%	0.000 (S)
TC $_{avg}$ (Cal/kg/day)		19.33±3.41	19.79±3.56	18.62±3.06	0.208 (NS)
Cal Level $_{avg}$	Low level (<25 Cal/kg/day)	154 (94.48%)	90 (90.91%)	64 (100 %)	0.013 (S)
	Standard level (25-30 Cal/kg/day)	9 (5.52%)	9 (9.09%)	0 (0.00%)	
	High level (>30 Cal/kg/day)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
TC $_{avg}$ (Cal/day)		1327.32±261.96	1357.56±270.23	1280.54±243.32	0.581 (NS)

Values are presented as mean±SD, median (range), or number (%).
S: Significant (P-Value <0.05).
NS: Nonsignificant (P-Value >0.05).
mcg: microgram.
min: Minute.
GCS: Glasgow coma scale.
ALB: Albumin level.

1: Baseline after ICU admission.
2: 1 week after ICU admission.
1wk: Over 1 week of ICU admission.
avg: Average.
Δ: Changes of variable over time (1 week in this study).
Cal: Kcal.
TC: Total calories.
Kg: Kilogram.

Logistic regression analysis

In the univariate analyses, Child-Pugh score (5-15), Human Albumin Dose $_{avg}$, ALB_1, ALB_2, and % Δ ALB_{1wk}showed statistically significant associations with an overall 28-day ICU mortality. After adjusting for these variables, only the Human Albumin Dose

$_{avg}$, ALB_2, and % Δ ALB_{1wk}still showed an association with an overall 28-day ICU mortality.

The odd ratios (ORs) of all-cause in 28-day ICU mortality events are shown in Table 3.

Table 3. ORs for all-cause in 28-day ICU mortality events.

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (Yrs)	0.99	0.96-1.03	0.78 (NS)	----	-----	-----
Gender (Male)	1.13	0.57-2.24	0.72 (NS)	----	-----	-----
BMI (Kg/m²)	0.96	0.84-1.04	0.28 (NS)	----	-----	-----
Child-Pugh score (5-15)	0.17	0.06-0.45	0.00 (S)	3.38	0.00- #	0.971 (NS)
Pre-ICU admission days ($day_{(s)}$)	#	0.00- #	0.988 (NS)	-----	-----	-----
TC (Cal/day)	0.99	0.99-1.00	0.07 (NS)	-----	-----	-----
Human Albumin Dose $_{avg}$ (g/day)	0.81	0.75-0.87	0.00 (S)	0.14	0.03-0.76	0.020 (S)
ALB_1 (g/dl)	47.06	10.50-210.91	0.00 (S)	#	0.00- #	0.442 (NS)
ALB_2 (g/dl)	0.01	0.00-0.15	0.00 (S)	0.00	0.00- #	0.035 (S)
% Δ ALB_{1wk} (%)	0.66	0.58-0.75	0.00 (S)	0.16	0.00- #	0.021 (S)

OR, odds ratio.
CI, confidence interval.
BMI: Body mass index.
ALB: Albumin level.
1: Baseline value (at ICU admission) of prognostic indicator.
2: Prognostic value on day 7 (1 week after ICU admission).
1wk: Over 1 week of ICU admission.
avg: Average.
g: Gram.
Yrs: Years.
Δ: Changes of variable over time (1 week in this study).
Cal: Kcal.
TC: Total calories.
#: Extremely large number.

Prognostic values of the ALB_2 and %Δ ALB_{1wk}.

The AUC of the %Δ ALB_{1wk} (0.929; 95% CI, 0.885-0.972) was significantly greater than that of ALB_1 (0.266; 95% CI, 0.184-0.349) and ALB_2 (0.655; 95% CI, 0.568-0.743). The ROC curve analysis is shown in Figure 1. Table 4 shows the optimal cutoff points, sensitivity (TPR), specificity (TNR), youden's index (YI) or performance, positive and negative predictive values (PPV and NPV), accuracy index, and the expected 28-day ICU mortality rate of critically ill patients based on this study's binary logistic regression models. The best cutoff values of the ALB_2 and the %Δ ALB_{1wk} in this study are 2.65 and -6.31%, respectively. The correlation between 28-day ICU mortality and the two significant prognosticators (ALB_2 and %Δ ALB_{1wk}) are illustrated in Figure 2 and Figure 3.

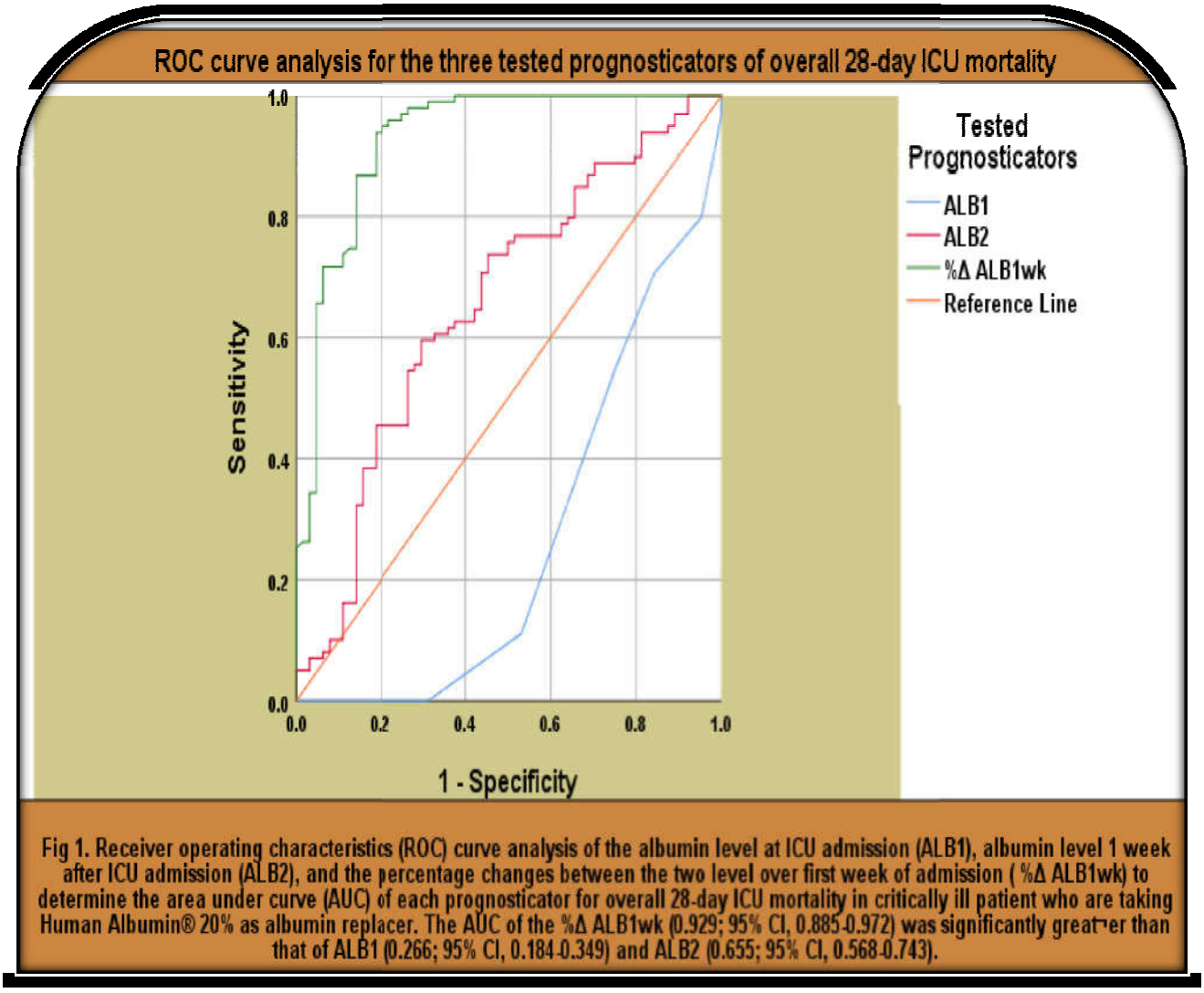

Fig 1. Receiver operating characteristics (ROC) curve analysis of the albumin level at ICU admission (ALB1), albumin level 1 week after ICU admission (ALB2), and the percentage changes between the two level over first week of admission (%Δ ALB1wk) to determine the area under curve (AUC) of each prognosticator for overall 28-day ICU mortality in critically ill patient who are taking Human Albumin® 20% as albumin replacer. The AUC of the %Δ ALB1wk (0.929; 95% CI, 0.885-0.972) was significantly greater than that of ALB1 (0.266; 95% CI, 0.184-0.349) and ALB2 (0.655; 95% CI, 0.568-0.743).

Table 4. Sensitivity, specificity, positive and negative predictive values, youden's and accuracy indices, and expected % 28-day ICU mortality of the two significant prognosticators in this study's critically ill patients.

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	AI	% Mortality*
ALB_2	2.65	59.59%	29.69%	29.91%	70.31%	56.48%	72.91%	66.10%	34.93%
$\%\Delta\ ALB_{1wk}$	-6.31%	93.94%	18.75%	75.19%	81.25%	76.41%	95.40%	86.23%	58.42%

ALB: Albumin level.
1wk: Over 1 week of ICU admission
Δ: Changes of variable over time (1 week in this study).
TPR: True positive rate (sensitivity)
FPR: False positive rate.
YI: Youden's index or performance.
TNR: True negative rate (Specificity).
PPV: Positive predictive value.
NPV: Negative predictive value.
AI: Accuracy index.
Mortality*: Overall 28-day ICU mortality.

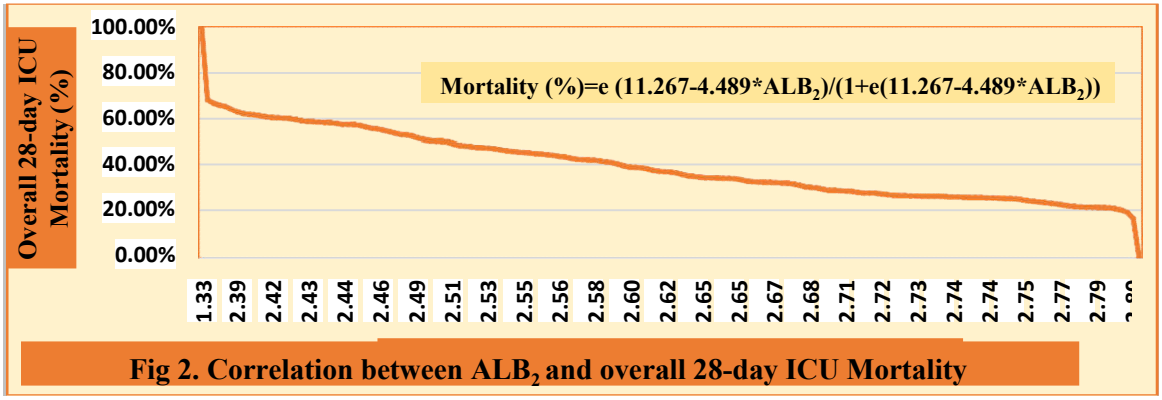

Fig 2. Correlation between ALB_2 and overall 28-day ICU Mortality

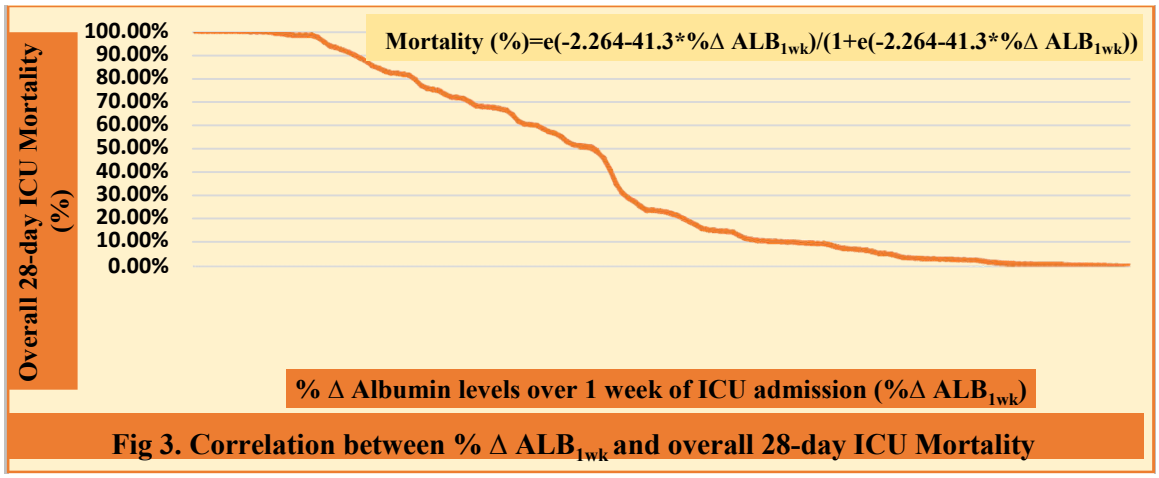

Fig 3. Correlation between % Δ ALB_{1wk} and overall 28-day ICU Mortality

DISCUSSION

Hypo-albuminemia has long been a predictor of poor outcome, such as mortality, morbidity, and prolonged ICU and hospital days[8-10].There are many studies that low serum albumin concentration reflects disease severity and prognosis in critically ill adult patients[11-13].Unexpectedly, we showed that ALB_1 was significantly higher in nonsurvivors compared with survivors (2.94±0.39 vs 2.63±0.20, respectively; P<0.05) which provide us the positive impact of Human Albumin® 20% administration on critically ill patient's mortality and the importance of obtaining serial measurements of albumin levels due to instability and dynamic nature of critically ill patients. The average human albumin dose during first week of ICU admission was significantly higher in survivors than in nonsurvivors (18.89±3.16 vs 14.06±6.09, respectively; P<0.05) that ultimately resulted in significantly higher ALB_2 in survivors compared with nonsurvivors (2.64±0.12 vs 2.57±0.13, respectively; P<0.05) and significantly higher %Δ ALB_{1wk} in nonsurvivors than in survivors (-11.47%±8.23% vs 0.69%±4.61%, respectively; P<0.05). The best cutoff values of the ALB_2 and the %Δ ALB_{1wk} in this study are 2.65 and -6.31%, respectively. Which means that to minimize ICU patient's mortality with minimal cost expenditure, Human Albumin® 20% can be conservatively used to keep albumin level not less than 2.65 g/dl and the changes in albumin levels not to exceed 6.31%.

There are some limitations in the current study. First, this study was limited to the single center using the data collected retrospectively. Since serum albumin level in critically ill patients is also affected by transcapillary escaping, nutrition provision, CRP level, variable albumin synthesis, and albumin catabolism, this study was not able to evaluate the effect size of these confounders on overall critically ill patients. Therefore, further studies might be needed in a multicenter setting using prospective data.

In conclusion, comparison to ALB_1, the %Δ ALB_{1wk} and ALB_2 have a significantly prognostication which is a significantly higher in %Δ ALB_{1wk}than ALB_2 with a sensitivity and performance of (93.94% and 75.19% vs 59.59% and 29.91%, respectively; P<0.001). The %Δ ALB_{1wk} may serve a novel independent prognosticating indicator for critically ill patient's mortality who are taking human

albumin. Also, we concluded that Human Albumin® 20% can be conservatively used to keep albumin level not less than 2.65 g/dl and the changes in albumin levels not to exceed 6.31% in order to minimize the critically ill patient's mortality with a reasonable acquisition cost.

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