



## THE CORRELATION BETWEEN EARLY PROTEIN DENSITY PROVISION AND 28-DAY OVERALL MORTALITY IN CRITICALLY ILL PATIENTS WHO ARE TAKING STANDARD ENTERAL NUTRITIONAL FORMULAS

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### ABSTRACT:

**Objectives:** Early appropriate enteral calories and proteins are essential for critically ill patients due to universally extensive loss of total body protein mass during critical illness. The objective of this study was to test the inverse correlation and positive prognostic efficacy between average protein density input enterally during first week of ICU admission ( $PD_{avg}$ ) and 28-day overall ICU mortality.

**Methods:** We performed a retrospective analysis of patients admitted to our adult ICU between April 2017 and Sep 2018. Patients were excluded if they discharged or died before 1 week of ICU admission. A receiver operating characteristic (ROC) and sensitivity analysis were conducted to test the predictive ability and optimal cutoff point of  $PD_{avg}$  for critically ill patients who were taking Ensure<sup>®</sup>, Nutrison<sup>®</sup>, or Resource<sup>®</sup> Optimum.

**Results:** A total of 163 critically ill patients were finally included in this study. The mean age was  $58.37 \pm 9.96$  years, and 112 (68.71%) were male. The overall 28-day ICU mortality rate was 39.26% (64 patients). The  $PD_{avg}$  was significantly higher in survivors than in nonsurvivors ( $3.72 \pm 0.74$  vs  $3.50 \pm 0.36$ ;  $P < 0.05$ ). The prognostic value of the  $PD_{avg}$  to predict overall 28-day ICU mortality was 0.663; 95% CI, 0.579 to 0.748.

**Conclusion:** Early protein density input enterally during first week of ICU admission has an inverse correlation and a significant predictive capability with 28-day overall ICU mortality. In order to minimize the critically ill patient's mortality as possible, we must use an enteral formula with PD not less than 3.53 g/100 Cal.

**KEY WORDS:** Protein density, Critical, Mortality, Malnutrition.

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## INTRODUCTION

Early appropriate calories and proteins provision through enteral nutrition are essential for critically ill patients due to universally extensive loss of total body protein mass during critical illness<sup>1-4</sup>. Loss of up to 18% of muscle mass is expected in the first 10 days of intensive care unit (ICU) admission in order to provide the required amino acids for synthesis of acute-phase proteins and immunoglobulins<sup>5-9</sup>. This rate of muscle protein catabolism can be minimized by early provision of an appropriate protein density through either enteral or parenteral feeding<sup>10-12</sup>. As a result of increasing need to establish a simplified mortality prognostic index for early stratification of ICU patients<sup>13</sup>, we evaluated the inverse correlation and positive predictive efficacy between  $PD_{avg}$  and 28-day overall ICU mortality. This study also aimed to determine the optimal cutoff point and the mortality prognosticator performance. We hypothesized that this  $PD_{avg}$  could be used as surrogate independent predictor and as novel prognosticator for critically ill patient's mortality.

## METHODS

### Study design and setting

This single-center retrospective study was 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. Table 1 shows the inclusion/exclusion and data collection criteria of our study's critical ill patients.

### Statistical analysis

Patient's continuous variables was expressed as mean  $\pm$  standard deviation by using the Mann-Whitney U test and the independent samples T-test while categorical variables was expressed as numbers with percentages or medians (interquartile ranges) by using  $\chi^2$  test. Univariate analysis was conducted first followed by multivariate logistic regression for most possible affected patient's variables associated with ICU mortality analysis and values were compared for the two tested groups (survivors vs nonsurvivors). A receiver operating characteristic (ROC) curve followed by sensitivity analysis were generated to determine the area under the curve (AUC), predictive performance, and the optimal cutoff values for  $PD_{avg}$ . Youden's index, sensitivities, specificities, positive and negative predictive values, and accuracy index were also calculated. Binary logistic regression model was used to generate a  $PD_{avg}$  predictive equation for overall 28-day ICU mortality. Overall 28-day critically ill patient's survival curve was plotted using Kaplan Meier survival analysis. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values  $\leq 0.05$  were considered statistically significant.

**Table 1: Inclusion / Exclusion and collection data criteria of the study's critically ill patients.**

<b>Inclusion criteria</b>
Baseline demographics and anthropometrics, number of co-morbidities, primary cause of admission, pre-ICU and ICU admission days, Child-Pugh score data requirements, and average administered volume of enteral standard nutritional formulas to calculate $PD_{avg}$ and $TC_{avg}$ were known.
<b>Exclusion criteria</b>
Patients were excluded if they discharged or died before 1 week of ICU admission.
<b>Data collection</b>
Demographics and clinical data were collected from our EMRs. Nutritional parameters such as $TC_{avg}$ and $PD_{avg}$ were calculated from the total enteral nutritional formula volume administered during the first week of ICU admission. The primary outcome was overall 28-day ICU mortality. Survival to ICU discharge was defined as discharge from the ICU alive or dead.
<b>ICU: Intensive care unit.</b> <b>avg: avg: Average of variable input during first week of ICU admission.</b> <b>PD: Protein density.</b> <b>TC: Total calories.</b> <b>EMRs: Electronic medical records (Hakeem in our institution).</b>

**RESULTS:****Characteristics of the subjects**

Dropout processes of the study's participants are shown in Table 2.

**Table 2: Dropout processes of the critically illness study's cohort.**

<b>913 critically ill patients were admitted to our unit.</b>
<b>388 patients were excluded because they either discharged or died before 1 week.</b>
<b>362 patients were excluded because there data can't be obtained or incomplete.</b>
<b>Remaining 163 critically ill patients were finally included in this study.</b>

The mean age was  $58.37 \pm 9.96$  years, and 51 subjects (31.29%) were female. 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 3 and Table 4, respectively. The  $PD_{avg}$  was significantly higher in survivors than in nonsurvivors ( $3.72 \pm 0.74$  vs  $3.50 \pm 0.36$ ;  $P < 0.05$ ).

**Table 3: Demographics / Admission co-morbidities and diagnostics / Anthropometrics comparison of study's ICU patients.**

Variables		Total (n=163)	Survivors (n=99)	Nonsurvivors (n=64)	P-Value
Age (Yrs)		$58.37 \pm 9.96$	$58.55 \pm 9.948$	$58.09 \pm 10.053$	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))		$4.27 \pm 3.91$	$2.23 \pm 1.06$	$7.42 \pm 4.57$	0.000 (S)
ICU Stay day(s)		$12.40 \pm 4.79$	$9.23 \pm 1.06$	$17.30 \pm 4.14$	0.000 (S)
Hospital Stay day(s)		$16.67 \pm 6.81$	$11.46 \pm 2.12$	$24.72 \pm 1.98$	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 <sub>1</sub> (Kg)		$74.17 \pm 10.24$	$74.63 \pm 10.06$	$73.45 \pm 10.56$	0.609 (NS)

<b>IBW<sub>1</sub> (Kg)</b>		64.97±6.90	64.60±6.77	65.56±7.12	0.813 (NS)
<b>AdjBW<sub>1</sub> (Kg)</b>		68.65±6.16	68.61±6.18	68.72±6.18	0.908 (NS)
<b>BMI<sub>1</sub> (Kg/m<sup>2</sup>)</b>		25.92±4.00	26.19±3.85	25.50±4.22	0.311 (NS)
<b>28-day ICU Survival</b>		99 (60.74%)			
<b>28-day ICU Mortality</b>	<b>Overall Mortality</b>	64 (39.26%)			
	<b>Early Mortality (≤14 days)</b>	16 (9.82%)			
	<b>Late Mortality (&gt;14 days)</b>	48 (29.45%)			
<p>Values are presented as mean±standard deviation or number (%).</p> <p>n: Number of study's critically ill patient participants.</p> <p>ICU: Intensive care unit.</p> <p>S: Significant (P-Value &lt;0.05).</p> <p>NS: Nonsignificant (P-Value &gt;0.05).</p>		<p><b>IBW: Ideal body weight.</b></p> <p><b>AdjBW: Adjusted body weight.</b></p> <p><b>1: Baseline after ICU admission.</b></p> <p><b>2: 1 week after ICU admission.</b></p> <p><b>BMI: Body mass index.</b></p> <p><b>BW: Body weight.</b></p>			

**Table 4: Baseline and follow-up data comparison of study's critically ill patients.**

Variables		Total (n=163)	Survivors (n=99)	Nonsurvivors (n=64)	P-Value
<b>Child-Pugh Score<sub>1</sub> (5-15)</b>		6 (6-8)	6 (6-8)	6 (6-7)	0.088 (NS)
<b>Liver severity<sub>1</sub></b>	<b>Normal/At Risk (5-6)</b>	124 (76.07%)	70 (70.71%)	54 (84.38%)	0.065 (NS)
	<b>Moderate (7-9)</b>	38 (23.93%)	28 (28.28%)	10 (15.63%)	
	<b>Severe (10-15)</b>	0 (0.00%)	0 (0.00%)	0 (0.00%)	
<b>PD<sub>avg</sub> (g/100Cal/day)</b>		3.64±0.63	3.72±0.74	3.50±0.36	0.002 (S)
<b>PD Strength</b>	<b>Low Strength (1-2.9 g/100Cal)</b>	15 (9.20%)	8 (8.08%)	7 (10.94%)	0.123 (NS)
	<b>Standard Strength (3-3.9 g/100 Cal)</b>	119 (73.01%)	70 (70.71%)	49 (76.56%)	
	<b>Moderate Strength (4-4.9 g/100 Cal)</b>	20 (12.27%)	12 (12.12%)	8 (12.50%)	
	<b>High Strength (5-6.9 g/100 Cal)</b>	9 (5.52%)	9 (9.09%)	0 (0.00%)	
	<b>Very high Strength (≥7 g/100 Cal)</b>	0 (0.00%)	0 (0.00%)	0 (0.00%)	
<b>Protein Dose<sub>avg</sub> (g/day)</b>		35.01±14.56	37.95±17.09	30.46±7.46	0.002 (S)
<b>% PC<sub>avg</sub> (%)</b>		10.29%±2.32%	10.84%±2.74%	9.45%±0.99%	0.000 (S)
<b>TC<sub>avg</sub> (Cal/kg/day)</b>		19.33±3.41	19.79±3.56	18.62±3.06	0.208 (NS)
<b>TC<sub>avg</sub> (Cal/day)</b>		1327.32±261.96	1357.56±270.23	1280.54±243.32	0.581 (NS)
<b>ENFs</b>	<b>Ensure<sup>®</sup></b>	99 (60.74%)	57 (57.58%)	42 (65.63%)	0.517 (NS)
	<b>Nutrison<sup>®</sup></b>	41 (25.15%)	27 (27.27%)	14 (21.88%)	
	<b>Peptamen<sup>®</sup> Resource</b>	23 (14.11%)	15 (15.15%)	8 (12.50%)	
<p>Values are presented as mean±standard deviation, median (range), or number (%).</p> <p>n: Number of study's critically ill patient participants.</p> <p>PD: Protein density.</p> <p>PC: Protein calories</p> <p>avg: Average of variable input during first week of ICU admission.</p>		<p><b>S: Significant.</b></p> <p><b>NS: Nonsignificant.</b></p> <p><b>Cal: Kcal.</b></p> <p><b>TC: Total calories.</b></p> <p><b>ENFs: Enteral nutritional formulas.</b></p>			

**Logistic regression analysis**

In the univariate analyses, Child-Pugh score (5-15) and PD<sub>avg</sub> showed statistically significant associations with an overall 28-day ICU mortality. After adjusting for these variables, only the PD<sub>avg</sub> 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 5.

**Prognostic values of the PD<sub>avg</sub>.**

The prognostic value of the PD<sub>avg</sub> to predict overall 28-day ICU mortality is 0.663; 95% CI, 0.579 to 0.748. The ROC curve analysis are shown in

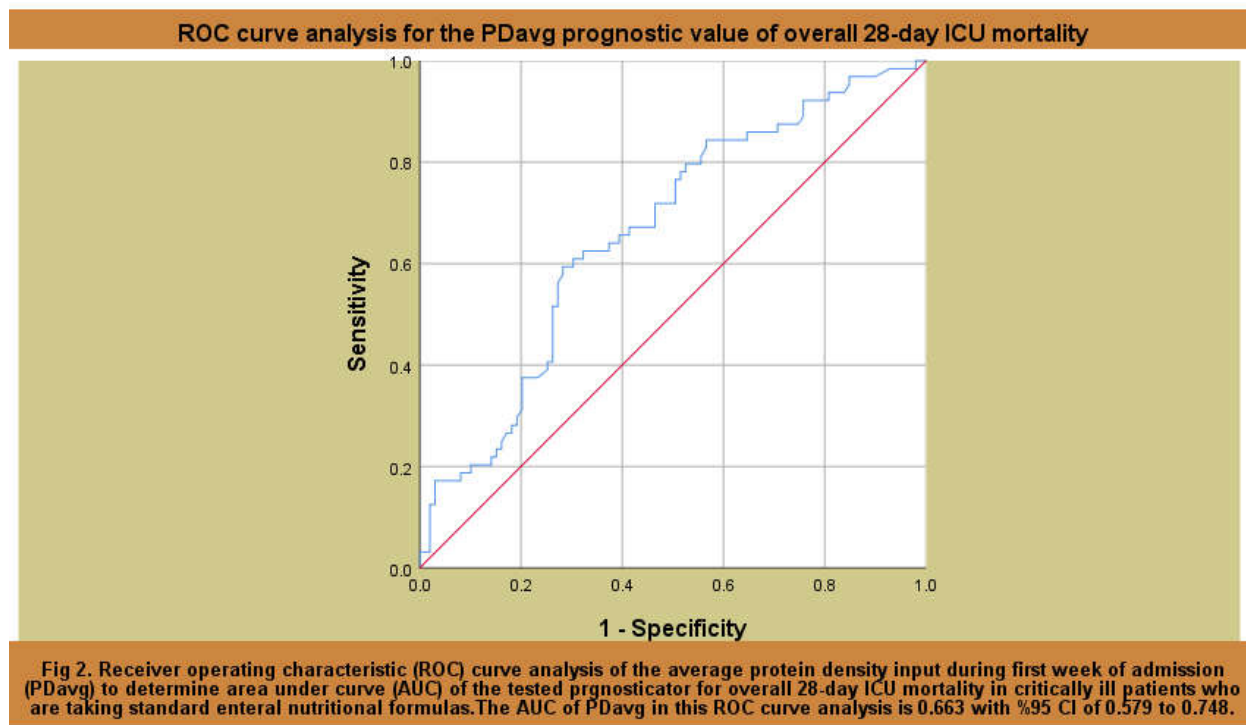
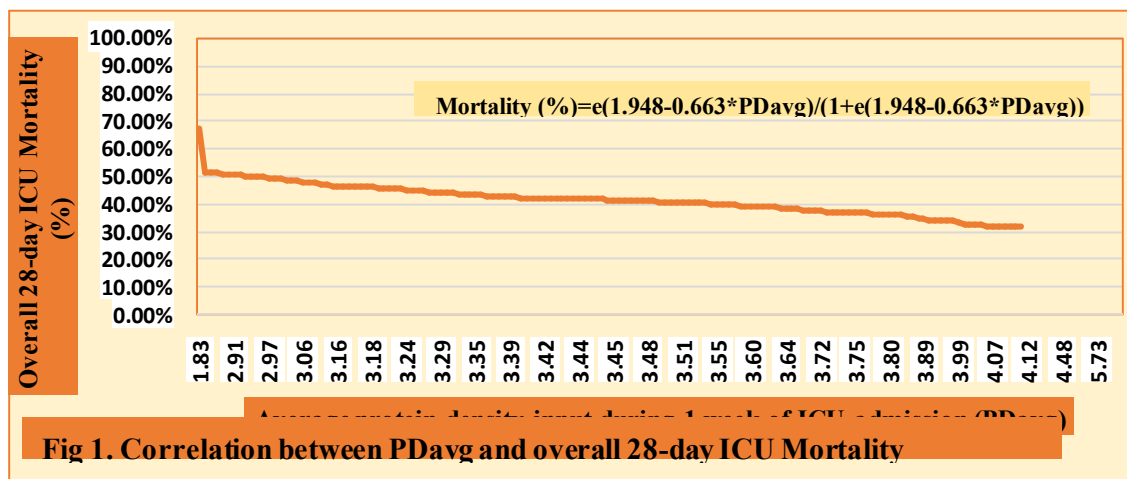
Figure 1. Table 6 shows the optimal cutoff point, sensitivity (TPR), specificity (TNR), youden's index (YI) or performance, positive and negative predictive values (PPV and NPV), accuracy index, and the expected 28-day ICU mortality rate of critically ill patients based on this study's binary logistic regression models. The best cutoff value of the PD<sub>avg</sub> in this study was 3.53. The correlation between 28-day ICU mortality and the PD<sub>avg</sub> values are illustrated in Figure 2. The plotted survival curves between individual protein density strengths (Low, Standard, Moderate, and High) and overall 28-day ICU survival are shown in Fig 3.

**Table 5: ORs for all-cause in-ICU mortality events**

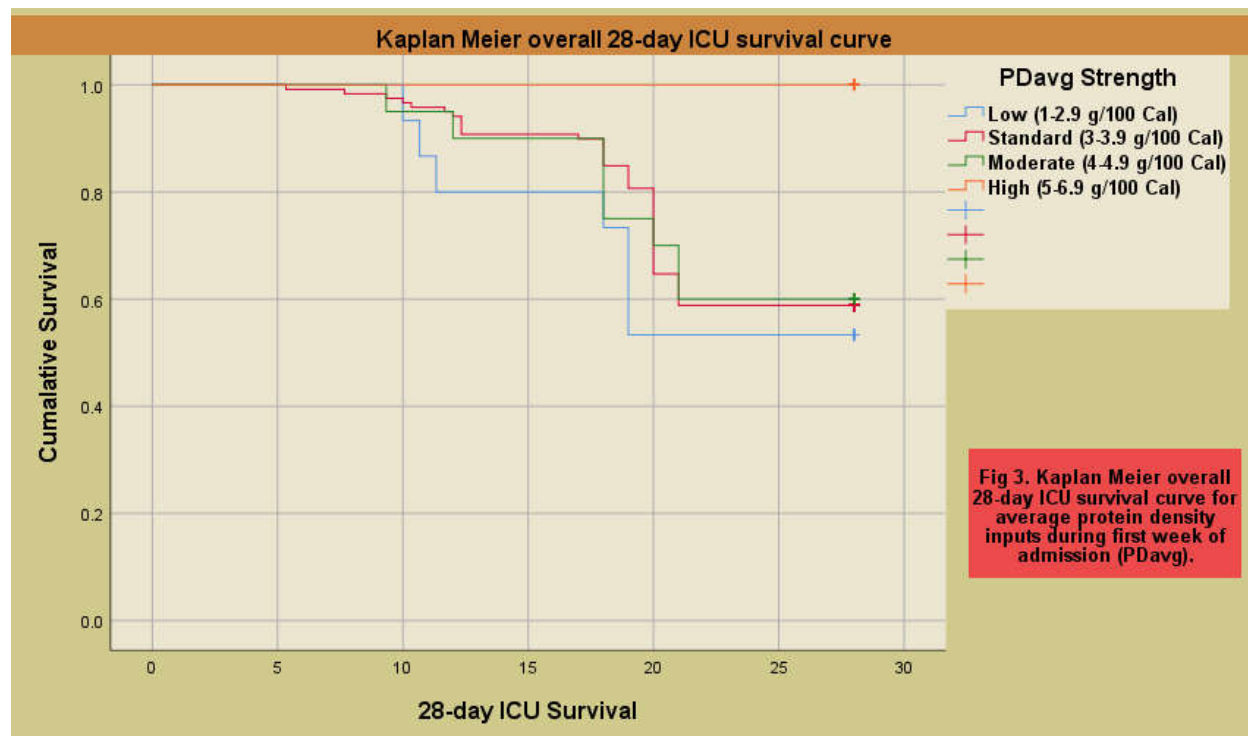
Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (Yrs)	0.99	0.96-1.03	0.78 (NS)	----	----	----
Gender (Male)	1.13	0.57-2.24	0.72 (NS)	----	----	----
BMI (Kg/m <sup>2</sup> )	0.96	0.84-1.04	0.28 (NS)	----	----	----
Child-Pugh score (5-15)	0.17	0.06-0.45	0.00 (S)	3.38	0.00- #	0.97 (NS)
PD <sub>avg</sub> (g/100 Cal/day)	0.52	0.28-0.97	0.04 (S)	0.00	0.00-0.12	0.01 (S)
TC (Cal/day)	0.99	0.99-1.00	0.07 (NS)	----	----	----
OR, odds ratio. BW: Body weight. BMI: Body mass index. PD <sub>avg</sub> : Protein density input during 1 week of ICU admission.			Cal: Kcal. TC: Total calories. #: Extremely large number. CI, confidence interval.			

**Table 6: Sensitivity, specificity, positive and negative predictive values, youden's and accuracy indices, and expected % 28-day ICU mortality of PD<sub>avg</sub> in this study's critically ill patients.**

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	AI	%Mortality*
PD <sub>avg</sub> (g/100 Cal/day)	3.53	51.50%	35.9%	15.60%	64.1%	48.12%	67.15%	75.6%	40.30%
PD <sub>avg</sub> : Average of protein density input during 1 week of ICU admission. 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.				







## DISCUSSION

The relationship between protein provision and protein catabolism in ICU is unclear<sup>14-15</sup>. However, while it appears that catabolism may not be diminished by nutrition provision, possibly protein synthesis is able to be influenced<sup>16-18</sup>. Protein catabolism has long been a predictor of poor outcome, such as mortality, morbidity, and prolonged ICU and hospital days<sup>19</sup>. As expected, we showed that PD<sub>avg</sub> was significantly higher in survivors compared with nonsurvivors ( $3.72 \pm 0.74$  vs  $3.50 \pm 0.36$ ;  $P < 0.05$ ) which provide us the positive impact of early protein and calories provision on critically ill patient's mortality. The optimal cutoff values of the in this study is 3.53 g/100 Cal. Which means that to minimize the critically ill patient's mortality as possible, we must use an enteral formula with PD not less than 3.53 g/100 Cal.

There are some limitations in the current study. First, this study was limited to the single center using the data collected retrospectively. PDavg in this

study is inadequate for most critically ill patients to test the actual positive impact of protein on mortality or other clinical outcomes. Therefore, further studies might be needed in a multicenter setting using prospective data and the protein gaps must be filled with separate modular protein formulas.

In conclusion, early protein density input enterally during first week of ICU admission has an inverse correlation and a significant predictive accuracy with 28-day overall ICU mortality. Significant PD<sub>avg</sub> prognostication has a sensitivity and performance of (51.50% and 15.60%, respectively). The PD<sub>avg</sub> may serve a novel independent prognosticating indicator for critically ill patient's mortality who are taking standard enteral nutritional formulas such as; Ensure<sup>®</sup>, Nutrison<sup>®</sup>, Peptamen<sup>®</sup> Resource.. Also, we concluded that to minimize the critically ill patient's mortality as possible with a reasonable acquisition cost, we must always keep PD<sub>avg</sub>  $\geq 3.53$  g/100 Cal.

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