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The Clinical Impacts of Using Modular Protein Formulas in Critically Ill Patients Who are Taking Standard Enteral Nutritional Formulas

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***Abstract*— *Objectives**: Most critically ill patients are under stress conditions from a variety of insults, which are primarily characterised by protein hypercatabolism to fuel the organs of the body and sustain life. The aim of this study was to evaluate the clinical impacts of using available modular protein formulas (e.g. PROSource®TF or Whey Protein 100% Powder) to increase protein provision in critically ill patients who were using standard formulas. **Methods:** We performed a retrospective analysis of 75 patients admitted to the adult Intensive Care Unit between April 2017 and January 2019 for whom nutritional and non-nutritional data were known. All continuous variables for patients were expressed as the Mean±SD by using the independent samples T-test, while categorical and ordinal variables were expressed as numbers with percentages by using the Chi square test or as a median (interquartile range) using the Mann-Whitney U test, respectively. Analysis values were compared for the two tested groups (survivors vs. non-survivors) and the non-survival group was further analysed after being divided into 2 subgroups, early and late mortality. **Results:** The mean overall age was 56.92±9.55 years and 50 subjects (66.66%) were male. The early, late, and overall 28-day ICU mortality rates were 6.67%, 16%, and 22.67%, respectively. Baseline pre-ICU admission days, ICU stay days, and overall hospital stay days were significantly higher in non-survivors than in survivors (8.88±3.52 days, 15.82±3.86 days, and 24.71±0.77 days vs. 2.81±1.42 days, 9.81±1.42 days, and 12.62±2.84 days, respectively). Ventilation-free days were significantly higher in survivors than non-survivors (5.75±1.03 days vs. 2.04±1.44 days). Albumin was significantly higher in survivors than in non-survivors (3.93±0.49 g/dl vs. 2.73±0.89 g/dl) with a mean difference of +1.08±0.43 g/dl. **Conclusion:** Modular protein formulas like PROSource®TF or reconstituted whey protein powder are effective at increasing or at least stabilising serum albumin levels in critically ill patients and combating the hypercatabolic state in order to decrease ventilator free days, overall hospital length of stay, early and late mortality, and overall 28 day-ICU mortality.*

***Keywords*—** *Critically ill patients, Enteral feeding, Modular protein formulas, Mortality, Overfeeding, Protein density, Protein provision, Standard formulas.*

I. INTRODUCTION

Physiologically, most critically ill patients are under stress conditions from a variety of effectors, which are primarily characterised by protein hypercatabolism to fuel the organs of the body and sustain life. In the setting of sustained and excessive protein breakdown, lean body wasting, hypo-albuminaemia, delayed wound healing and weaning from ventilators, and a higher risk of mortality are expected.[1-4] Most of the available standard enteral nutritional formulas (ENFs), either Ensure® or Resource® Optimum, are characterised by a standard protein density (PD) below 4 g /100 Cal, which may cause overfeeding if there is an attempt to achieve the high protein requirements of critically ill patients.[5-10] The aim of this study was to evaluate the clinical impacts of using available modular protein formulas (MPFs), either PROSource®TF or Whey Protein (WP) 100% Powder, to increase protein provision in critically ill patients who are using standard ENFs. The following measurements were made: average serum albumin levels during the first week of intensive care unit (ICU) admission (ALB_{avg}), and any changes (ΔALB), ICU and overall length of stay (LOS), ventilation free days (VFDs), early mortality (≤14 days), late mortality (>14 days), and overall 28-day ICU mortality.

II. METHODS AND MATERIALS

This was a single-centre observational retrospective study conducted in the Adult ICU of King Hussein Medical Hospital (KHMH) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and the requirement for consent was waived owing to its retrospective design. The study included a 75 critically ill patients admitted to our adult ICU via the emergency department (ED) or other hospital wards with any medical or surgical problem. The flow chart of critically ill patient selection and the data collection process is illustrated in Figure 1. The continuous variables of all patients were expressed as the Mean±SD by using the independent samples T-test, while categorical and ordinal variables were expressed as numbers with percentages by using the χ^2 test. Analysis values were compared for the two tested groups (survivors vs. non-survivors) and the non-survival group was further analysed after being divided into 2 subgroups, early and late mortality. All statistical analyses were performed using IBM SPSS ver.

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25 (IBM Corp., Armonk, NY, USA); P-values ≤0.05 were considered statistically significant.

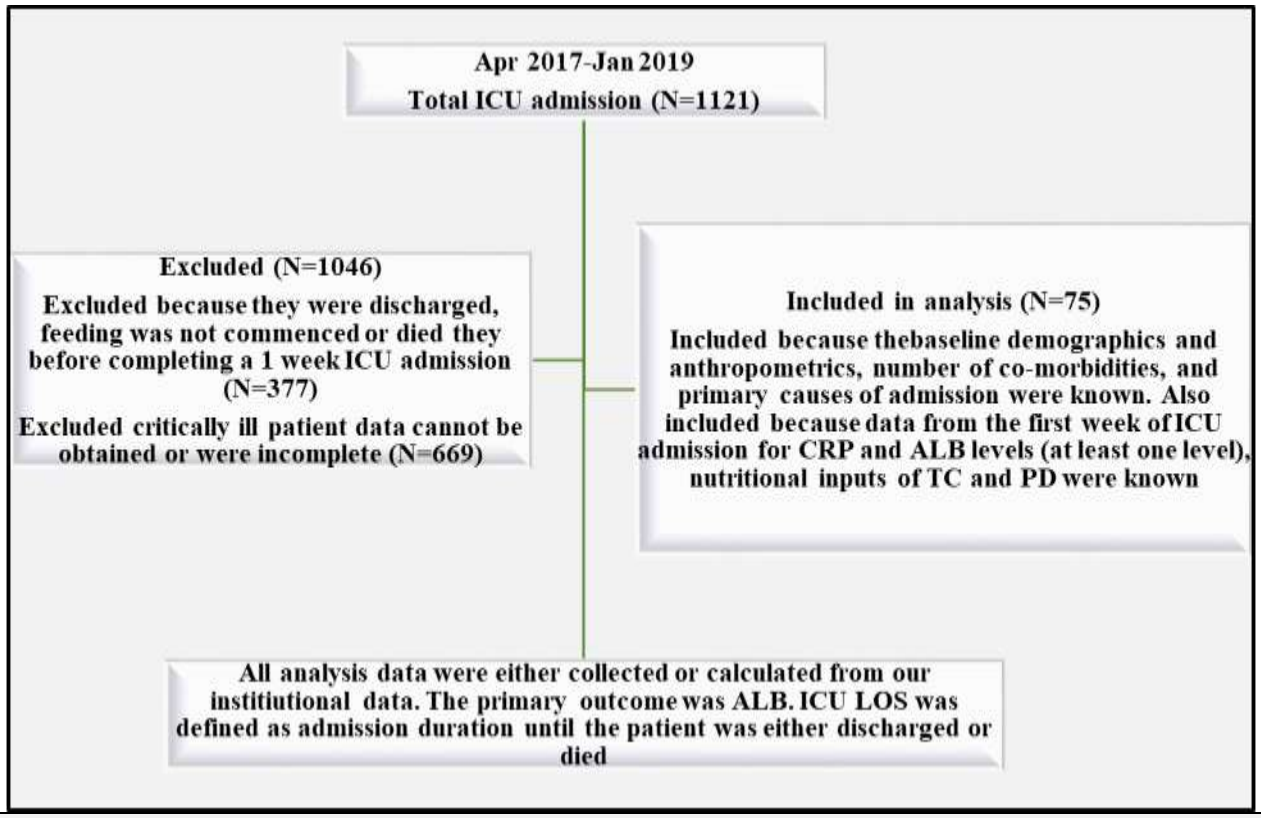

Fig 1. Flow chart of critically ill patient's selection and data collection process.
Apr: April CRP: C-reactive protein PD: Protein density
Jan: January LOS: Length of stay ALB: Albumin
ICU: Intensive Care Unit TC: Total calorie

III. Results

The mean overall age was 56.92±9.55 years. 50 subjects (66.66%) were male and 25 subjects (33.33%) were female. The early, late, and overall 28-day ICU mortality rates were 6.67%, 16%, and 22.67%, respectively. Baseline pre-ICU admission days, ICU stay days, and overall hospital stay days were significantly higher in non-survivors than in survivors (8.88±3.52 days, 15.82±3.86 days, and 24.71±0.77 days vs. 2.81±1.42 days, 9.81±1.42 days, and 12.62±2.84 days, respectively). Despite $PaCO_2$ being insignificantly higher in non-survivors than in survivors (50.62±2.74 mmHg vs. 49.73±2.05 mmHg, respectively), VFDs were significantly higher in survivors than non-survivors (5.75±1.03 days vs. 2.04±1.44 days, respectively). There were insignificant nutritional input differences between survivors and non-survivors regarding ENF and MPF Vol_{avg}, average total calories (TC_{avg}), PD_{avg}, and percentage of nutritional and non-nutritional calories from the total calories input (%NC_TC and % NNC_TC, respectively). Also, the ratio between carbohydrates and lipids (gCarb: gLipid ratio), and ALBavg were significantly higher in survivors than in non-survivors (3.93±0.49 g/dl vs. 2.73±0.89 g/dl, respectively) with a mean difference of +1.08±0.43 g/dl. Demographics, admission co-morbidities and classes, anthropometrics, and follow-up comparison data of the study's critically ill patients are summarised in Tables 1-2.

IV. Discussion

This study included mechanically and non-mechanically ventilated critically ill patients who had received standard ENFs with an average volume of 1314.18±361.44 ml/day. Either Ensure® (67%) or RESource®Optimum (33%) were used as standard ENFs in our study. To the best of our knowledge, this is the first study to address the positive clinical impacts of MPFs regarding ΔALB level, LOS, VFDs, early and late mortality, and overall 28-day ICU mortality when it is used as a protein supplement with standard ENFs in order to increase the provision of protein in these hypercatabolic patients. We proposed an average protein requirement in critically ill patients of around 100 g/day. Therefore, if the 100 g protein requirement is to be covered by using the available standard ENFs which have a PD of around 3.5 g/100 Cal, about 2800 ml/day (2800 Cal/day) must be provided, which will lead to an increased risk of fluid overload as well as an increase in the gastric residual volume (GRV) and subsequently increased risk of enteral nutrition intolerance and aspiration pneumonia.[11-12] Overfeeding is briefly defined as a respiratory quotient (RQ) exceeding 1 when the total calorie input exceeds the caloric expenditure. Overfeeding is

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the most common nutritional factor in critical care patients which impedes successful weaning from the ventilator, increases the LOS, increases the risk of the emergence of multi-drug resistant gram negative bacteria (MDR-GNB), and overall ICU mortality.[13-14] Mathematically, the lowest PD required in critically ill patients to minimise the risk of overfeeding is 5 g/100 Cal, taking into consideration average calorie and protein requirements of 2000 Cal/day and 100 g/day, respectively. In our study, $PaCO_2$ was insignificantly higher in non-survivors than in survivors (50.62±2.74 mmHg vs. 49.73±2.05 mmHg, respectively) and PD was insignificantly higher in survivors than in non-survivors (5.59±1.65 g/100 Cal vs. 4.77±1.59 g/100 Cal, respectively), while VFDs were significantly higher in survivors than in non-survivors (5.75±1.03 days vs. 2.04±1.44 days, respectively) and there was a subsequently significantly lower ICU LOS in survivors than in non-survivors (9.81±1.42 days vs. 15.82±3.86 days, respectively). Our explanation for these results is the PD value in survivors which exceeds 5 g/100 Cal though it is not statistically significant. After careful analysis of the data, ALB was significantly increased by +1.32±0.36 g/dl in survivors in comparison with only +0.24±0.79 g/dl in non-survivors despite the insignificant differences between survivors and non-survivors ENFs and MPFs volume inputs. Our explanation for the significant differences in ALB levels is the strong correlation between C-reactive protein (CRP) and ALB.[15-19] ALB catabolism and the rate of escape from the intravascular compartment are directly related to the CRP level, while the rate of synthesis of ALB is inversely related to the CRP level. In our study, CRP and CRP:ALB ratio were significantly higher in non-survivors than in survivors (56.44±21.57 mg/dl and 23.03±9.71 vs. 33.15±16.77 mg/dl and 13.05±7.27, respectively).

TABLE 1. Baseline and follow-up comparison data between survivors and non-survivors

Variables		Total (n=75)	Survivors (n=58)	Non-survivors (n=17)	P-Value
Age (Yrs)		56.92±9.55	56.33±9.22	58.94±10.64	0.324 (NS)
Gender	Male	50 (66.66%)	38 (65.52%)	12 (70.59%)	0.004 (S)
	Female	25 (33.33%)	20 (34.48%)	5 (29.41%)	
Day(s) Pre-ICU admission (day(s))		4.19±3.28	2.81±1.42	8.88±3.52	0.000 (S)
ICU Stay $day_{(s)}$ ($Day_{(s)}$)		11.17±3.35	9.81±1.42	15.82±3.86	0.000 (S)
Hospital Stay day(s)		15.36±5.68	12.62±2.84	24.71±0.77	0.000 (S)
VFDs ($Day_{(s)}$)		4.91±1.93	5.75±1.03	2.04±1.44	0.000 (S)
PaCO2 (mmHg)		49.93±2.23	49.73±2.05	50.62±2.74	0.149 (NS)
BW_1 (Kg)		70.73±8.66	71.74±8.11	67.28±9.81	0.061 (NS)
BMI_1 (Kg/m^2)		24.33±3.66	24.64±3.27	23.30±4.70	0.187 (NS)
ALB_1 (g/dl)		2.58±0.14	2.61±0.13	2.49±0.11	0.001 (S)
ALB_{avg} (g/dl)		3.66±0.79	3.93±0.49	2.73±0.89	0.000 (S)
CRP_{Avg} (mg/dl)		38.43±20.34	33.15±16.77	56.44±21.57	0.000 (S)
CRP: ALB Ratio (X: 1)		15.31±8.87	13.05±7.27	23.03±9.71	0.000 (S)
ENF Vol_{avg} (ml/day)		1314.18±361.44	1317.01±374.95	1304.49±321.33	0.901 (NS)
MPF Vol_{avg} (ml/day)		415.83±368.99	428.74±377.60	371.79±345.13	0.579 (NS)
TC_{avg} (Cal/kg/day)		28.46±6.83	28.05±7.09	29.88±5.82	0.332 (NS)
TC_{avg} (Cal/day)		1932.19±492.27	1916.82±515.83	1984.63±411.19	0.621 (NS)
% NC_TC		83.34%±6.05%	83.87%±5.68%	81.55%±7.08%	0.166 (NS)
% NNC_TC		16.63%±6.04%	16.08%±5.62%	18.51%±7.17%	0.145 (NS)
% NNC_Dextrose		12.39%±5.47%	11.79%±4.97%	14.49%±6.64%	0.073 (NS)
% NNC_ Lipid		4.26%±1.36%	4.34%±1.47%	3.96%±0.87%	0.313 (NS)
∑ g PRO_{avg} (g/kg/day)		1.63±0.81	1.67±0.83	1.49±0.72	0.417 (NS)
∑ g PRO_{avg} (g/day)		110.79±56.96	114.29±58.89	98.88±49.54	0.330 (NS)
% PC_ TC		21.64%±6.65%	22.39%±6.59%	19.09%±6.39%	0.072 (NS)
PD_{avg} (g/100Cal/day)		5.41±1.66	5.59±1.65	4.77±1.59	0.072 (NS)
NPC: g N Ratio (X: 1)		102.65±41.99	97.23±37.59	121.11±51.48	0.038 (S)
% Carb Cal_ TC		47.49%±5.37%	46.72%±4.96%	50.10%±6.03%	0.021 (S)
% Lipid Cal_ TC		30.87%±3.85%	30.89%±3.69%	30.81%±4.47%	0.939 (NS)
g Carb: g Lipid Ratio (X: 1)		3.68±0.68	3.60±0.58	3.95±0.92	0.064 (NS)
28-day ICU Survival			58 (77.33%)		0.000 (S)
28-day ICU Mortality			17 (22.67%)		

Values are presented as mean±standard deviation or number (%)
Yrs: Years
Kg: Kilogram
m: Metre
BW_1: Actual body weight at admission
BMI_1: Body mass index at admission
VFDs: Ventilation free days
ALB: Albumin level
CRP: C-reactive protein
CRP: ALB: C-reactive protein to albumin ratio
ENFs: Enteral nutritional formulas
MPFs: Modular nutritional formulas
gN: Gram of nitrogen
1: baseline at admission
Avg: Average during first week of admission
ICU: Intensive care unit
S: Significant (P-Value <0.05)
NS: Non-significant (P-Value >0.05)
n: Number of study's critically ill patients
TC: Total calories
NC: Nutritional calories
NNC: Non nutritional calories
PRO: Protein
PD: Protein density
NPC: Non protein calories
Carb: Carbohydrates
Cal: Calories

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TABLE 2. Baseline and follow-up comparison data between Early and Late mortality Nonsurvivors

Variables		Non-survivors (n=17)	Early Mortality (≤14 days) (n=5)	Late Mortality (>14 days) (n=12)	P-Value
Age (Yrs)		58.94±10.64	60.33±9.37	55.60±13.85	0.421 (NS)
Gender	Male	12 (70.59%)	4 (80%)	8 (66.67%)	0.000 (S)
	Female	5 (29.41%)	1 (20%)	4 (33.33%)	
Day(s) Pre-ICU admission (day(s))		8.88±3.52	13.60±1.67	6.92±1.62	0.000 (S)
ICU Stay day$_{(s)}$ (Day$_{(s)}$)		15.82±3.86	10.40±0.55	18.08±1.62	0.000 (S)
Hospital Stay day(s)		24.71±0.77	24.00±1.23	25.00±0.00	0.142 (NS)
VFDs (Day$_{(s)}$)		2.04±1.44	0.00±0.00	2.88±0.59	0.000 (S)
PaCO2 (mmHg)		50.62±2.74	51.41±2.33	48.74±2.98	0.066 (NS)
BW$_1$ (Kg)		67.28±9.81	66.41±11.17	69.36±5.88	0.589 (NS)
BMI$_1$ (Kg/m^2)		23.30±4.70	23.27±5.42	23.38±2.82	0.966 (NS)
ALB $_1$ (g/dl)		2.49±0.11	2.49±0.08	2.49±0.12	0.851 (NS)
ALB$_{avg}$ (g/dl)		2.73±0.89	1.72±0.71	3.16±0.56	0.000 (S)
CRP $_{Avg}$ (mg/dl)		56.44±21.57	58.16±18.73	55.73±23.39	0.840 (NS)
CRP: ALB Ratio (X: 1)		23.03±9.71	23.51±8.63	22.83±10.49	0.900 (NS)
ENF Vol$_{avg}$ (ml/day)		1304.49±321.33	1384.21±189.71	1271.27±364.69	0.527 (NS)
MPF Vol$_{avg}$ (ml/day)		371.79±345.13	348.43±413.97	381.53±332.55	0.864 (NS)
TC$_{avg}$ (Cal/kg/day)		29.88±5.82	31.61±7.73	29.17±5.07	0.449 (NS)
TC$_{avg}$ (Cal/day)		1984.63±411.19	2151.28±505.36	1915.19±367.68	0.295 (NS)
% NC_TC		81.55%±7.08%	88.26%±6.60%	78.76%±5.31%	0.007 (S)
% NNC_TC		18.51%±7.17%	21.43%±5.26%	11.51%±6.53%	0.005 (S)
% NNC_Dextrose		14.49%±6.64%	17.27%±4.64%	7.83%±6.23%	0.003 (S)
% NNC_ Lipid		3.96%±0.87%	3.91%±1.17%	3.98%±0.78%	0.886 (NS)
∑ g PRO Input $_{avg}$ (g/kg/day)		1.49±0.72	1.46±0.68	1.49±0.77	0.915 (NS)
∑ g PRO Input $_{avg}$ (g/day)		98.88±49.54	98.92±46.12	98.87±52.88	0.999 (NS)
% PC_ TC		19.09%±6.39%	17.79%±4.59%	19.63%±7.12%	0.605 (NS)
PD$_{avg}$ (g/100Cal/day)		4.77±1.59	4.45±1.15	4.91±1.78	0.606 (NS)
NPC: g N Ratio (X: 1)		121.11±51.48	123.39±39.03	120.16±57.43	0.910 (NS)
% Carb Cal_ TC		50.10%±6.03%	48.17%±7.13%	50.91%±5.65%	0.412 (NS)
% Lipid Cal_ TC		30.81%±4.47%	34.04%±4.39%	29.47%±3.93%	0.051 (NS)
g Carb: g Lipid Ratio (X: 1)		3.95±0.92	4.19±0.78	3.38±1.07	0.098 (NS)
ICU Mortality	Overall Mortality		17 (22.67%)		
	Early Mortality (≤14 days)		5 (6.67%)		0.000 (S)
	Late Mortality (>14 days)		12 (16%)		

Values are presented as mean±standard deviation or number (%)
Yrs: Years
Kg: Kilogram
m: Metre
BW$_1$: Actual body weight at admission
BMI$_1$: Body mass index at admission
VFDs: Ventilation free days
ALB: Albumin level
CRP: C-reactive protein
CRP: ALB: C-reactive protein to albumin ratio
ENFs: Enteral nutritional formulas
MPFs: Modular nutritional formulas
gN: Gram of nitrogen
1: baseline at admission
Avg: Average during first week of admission
ICU: Intensive care unit
S: Significant (P-Value <0.05)
NS: Nonsignificant (P-Value >0.05)
n: Number of study's critically ill patients
TC: Total calories
NC: Nutritional calories
NNC: Non nutritional calories
PRO: Protein
PD: Protein density
NPC: Non protein calories
Carb: Carbohydrates
Cal: Calories

V. CONCLUSION

In summary, most standard ENFs have a PD lower than 4 g/100 Cal, which increases the risk of overfeeding, feeding intolerance, and fluid overload. If protein requirements are targeted which necessitate the importance of the provision of protein to fill the protein gap deficit that are highly expected in critically ill patients or using specialised ENFs have a PD of no less than 5 g/100 Cal. MPFs like PROSource®TF or reconstituted WP powder are effective for increasing or at least stabilising serum albumin levels in critically ill patients and combating the hypercatabolic state in order to decrease VFDs, LOS, early and late mortality, and overall 28 day-ICU mortality. This study is limited by its retrospective design, the use of single-centre data, and the inclusion of only ICU patients. Nonetheless, our centre is an experienced and high-volume unit, so our data may be useful for other centres. A larger, multisite, prospective study is needed to control for multiple confounders.

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