

Research Article

THE CLINICAL AND ECONOMIC IMPACTS OF USING HIGH CALORIC AND PROTEIN SPECIALIZED  
VERSUS STANDARD NUTRITIONAL ENTERAL FORMULAS IN  
HYPOALBUMENIC HOSPITALIZED PATIENTS

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ABSTRACT

**Objectives:** Most available standard enteral nutritional formulas (ENFs) are characterized by standard protein and caloric density (PD and CD) which may not conserve lean body mass (LBM) and albumin (ALB) from hypercatabolism without risks. The aim of this study is to evaluate the clinical and economic impacts of using moderate PD/high CD ENF (RenaMent®) compared with standard ENFs (Ensure® and Resource®Optimum) when used at least for 2 weeks.

**Methods:** We performed a retrospective analysis between April 2017 to Mar 2019 and patients were excluded if they discharged or died before completed 2 weeks admission. All patient's compared variables were analyzed by using either ANOVA or  $\chi^2$  test. Analysis values were compared for Group I (standard ENFs) and Group II (RenaMent®) and the Group I was further analysed after being divided into 2 subgroups (Ensure® vs Resource®Optimum).

**Results:** The mean overall age was 58.37±9.95 years and 224 subjects (68.7%) were male. The % $\Delta$ ALB was significantly higher in Group II than on Group I (46.67%±11.19% versus 20.11%±8.56% or 20.91%±4.71%). The overall hospital LOS and overall 28-day hospital mortality were significantly lower in Group II when compared with Group I (13.26±6.53 days vs 15.08±7.02 days or 14.40±6.88 days) and (28 (25.2%) vs 43 (39.4%) or 37 (34.9%)), respectively. Economically, the cost expenditure to increase ALB by 1 g/dl was significantly lower in Group II than in Group I (13.23±14.33 USD vs 60.73±32.14 USD or 47.86±25.31 USD).

**Conclusion:** In summary, using moderate PD/high CD ENF may have an overall positive clinical and economic impacts compared with standard ENFs in malnourished hypoalbumenic hospitalized patients.

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INTRODUCTION

Pathophysiologically, most hospitalized ill patients and especially critically ill patients have an elevated c-reactive protein (CRP) and are under stress-induced hypercatabolic conditions from a variety of insults, which are primarily characterized by lean body mass (LBM) and ALB hypercatabolism to fuel cells and sustain life as possible.<sup>[1-5]</sup> In this setting, lean body wasting (LBW), hypoalbuminemia, muscle weakness, delayed wound healing and weaning from ventilator, higher risk of mortality, and high cost burden are definitely expected.<sup>[6-11]</sup> Most available ENFs in our institution of King Hussein Medical Hospital (KMH) are standard formulas (e.g. Ensure® and Resource® Optimum) which are commonly characterized by PD of <4 g /100 Cal and CD of < 1.2 Cal/ml. lower PD means higher risk of overfeeding and higher risk of overhydration (if CD is also low) if the high protein (PRO) requirements of stressed patients are attempted

to achieved.<sup>[12-14]</sup> The primary aim of this study is to test and evaluate the clinical and economic impacts of using moderate PD/high CD new our institutional available modular specialized formulas (RenaMent®) for at least 2 weeks in compared with already available standard ENFs regarding the percentage changes in albumin level ( $\Delta$  ALB), percentage changes in CRP to ALB ratio (CRP:ALB), changes in Human Albumin® 20% consumption ( $\Delta$ H.ALB), cost effectiveness to increase ALB by 1 g/dl ratio (CER), percentage changes in body weight (% $\Delta$ BW), length of stay (LOS), and overall 28-day hospital mortality. Secondary aims of this study is to evaluate the differences between the two tested groups in terms of risk of edematous status (OD), gastrointestinal tolerance, and risk of diarrhea.

METHODS AND MATERIALS

This was a single-centre observational retrospective study conducted in KHMC at Royal Medical Services (RMS) in

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Jordan between April 2017 to Mar 2019. 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 cohort of malnourished hypoalbumemic hospitalized patients with any medical or surgical problem. The flow chart of patient selection and the data collection process is illustrated in Figure 1. Analysis values were compared for Group I (malnourished patients who were on standard ENFs) and Group II (malnourished patients who were on moderate PD/high CD MF) and the Group I was further analysed after being divided into 2 subgroups (Ensure<sup>®</sup> vs Resource<sup>®</sup>Optimum). The continuous variables of all patients were expressed as Mean±SD and as Mean difference±SEM by using the ANOVA, while ordinal variables were expressed as numbers with percentages by using the  $\chi^2$  test. All statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA); P-values  $\leq 0.05$  were considered statistically significant.

## RESULTS

The mean overall age was 58.37±9.95 years and 224 subjects (68.7%) were male. There were insignificant differences regarding non-critical versus critical admission wards and medical versus surgical admission diagnostics. Although the baseline ALB, CRP, H.ALB, and CRP:ALB and overall ENF administration days were insignificantly different among the tested groups, the % $\Delta$ ALB was significantly higher in malnourished hypoalbumemic patients who were on RenaMent<sup>®</sup> for at least 2 weeks (Group II) than on malnourished hypoalbumemic patients who were on either Ensure<sup>®</sup> or Resource<sup>®</sup>Optimum for at least 2 weeks (Group I) (46.67%±11.19% versus 20.11%±8.56% or 20.91%±4.71%). This significant higher % $\Delta$ ALB was also accompanied by significant lower of  $\Delta$ H.ALB and % $\Delta$ CRP:ALB (-16.29±5.89 g/day vs -8.36±4.98 g/day or -8.89±3.16 g/day) and (228.9%±335.8% vs 318.5%±267.2% or 307.2%±289.5%), respectively.

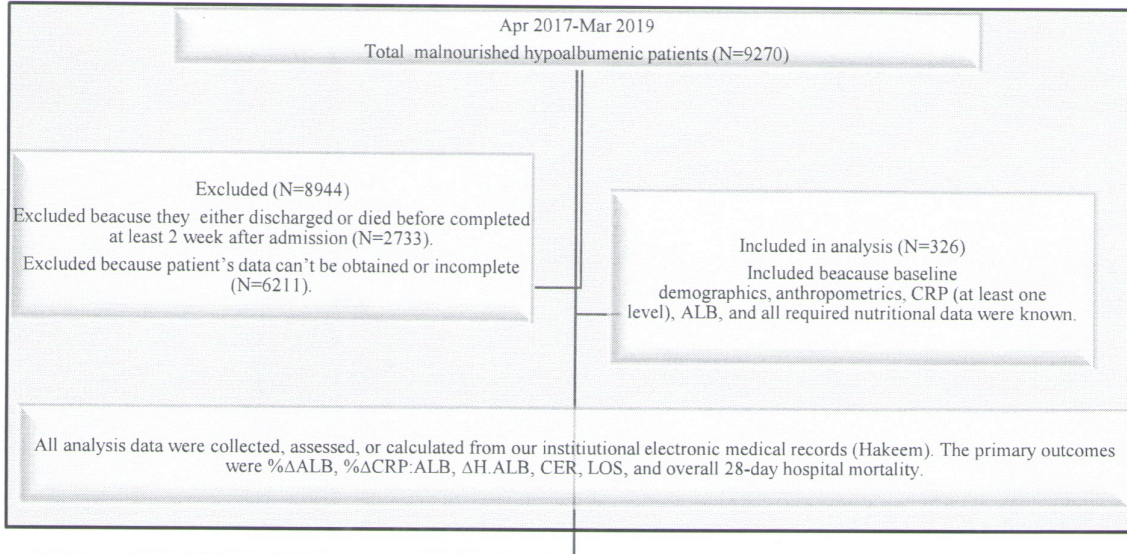
The overall hospital LOS and overall 28-day hospital mortality were significantly lower in Group II when compared with Group I (13.26±6.53 days vs 15.08±7.02 days or 14.40±6.88 days) and (28 (25.2%) vs 43 (39.4%) or 37 (34.9%)), respectively. Economically, the cost expenditure to increase ALB by 1 g/dl was significantly lower in Group II than in Group I (13.23±14.33 USD vs 60.73±32.14 USD or 47.86±25.31 USD) and significant cost saving of -47.50±3.39 USD (RenaMent<sup>®</sup> vs Ensure<sup>®</sup>) followed by -34.63±3.41 USD (RenaMent<sup>®</sup> vs Resource<sup>®</sup>Optimum) and -12.88±3.39 USD (Resource<sup>®</sup>Optimum vs Ensure<sup>®</sup>) taking into consideration that this significant CER differences includes only the cost of ENFs and cost of H.ALB and not includes other cost expenditures especially hospital LOS. Anthropometrically, tested cohort in Group II had significantly higher % $\Delta$ BW than tested cohort in Group I (3.79%±11.51% vs 2.45%±13.55% or 3.01%±14.37%). Subjectively, the ODs was mostly moderately improved in Group II (92 (85.2%)) and mostly slightly improved in edematous patients who were on Resource<sup>®</sup>Optimum subgroup of Group I (96 (88.9%)) while most of the hypoalbumemic edematous patient on Ensure<sup>®</sup> subgroup of Group I were insignificantly improved in ODs (72 (65.5%)). While there were significant differences in GIT ENF tolerance between the two groups and between the subgroups in which the incidence of <2 Symptoms (Sx) (e.g. bloating, cramping,  $\uparrow$  gastric residual volume (GRV), and

dyspepsia) was highest in Group II (77 (69.4%)) followed by Resource<sup>®</sup>Optimum subgroup of Group I (59 (55.7%)) and Ensure<sup>®</sup> subgroup of Group I (42 (38.5%)), there were insignificant differences among the tested groups regarding the risk of diarrhea. Although there were insignificant differences of GRV between the three tested ENFs, the rate of pro-kinetics consumption was significantly lowest in Group II (28 (25.23%) for Erythromycin and 24 (21.62%) for Metoclopramide) and highest in Ensure<sup>®</sup> subgroup of Group I (42 (38.53%) for Erythromycin and 31 (28.44%) for Metoclopramide). Demographics, admission diagnostics and wards, anthropometrics, nutritional indices and follow-up comparison data of the study's malnourished hypoalbumemic hospitalized ill patients are summarised in Tables 1-3.

## DISCUSSION

This study included malnourished hypoalbumemic hospitalized patients who had received intermittent ENFs with an average volume of 845.52±343.54 ml/day and frequency of 5.84±1.46 feed per day at average volume of 153.72±75.04 ml/feed. To the best of our knowledge, this is the first study directly compare the positive clinical and economic impacts of moderate PD/high CD EFs versus the standard PD/CD EFs. Due to the double CD of RenaMent<sup>®</sup> compared with either Ensure<sup>®</sup> or Resource<sup>®</sup>Optimum, patients in Group II had significantly lower average ENF daily volume (approximately half) than patients in Group I (574.93±190.54 ml/day vs 980.13±362.08 ml/day or 979.02±279.44 ml/day) and this is the primary explanation of the significant higher GIT tolerance/lower prokinetics consumption in Group II compared with both subgroups of Group I and also the major explanation of insignificant differences in GRV among the three tested ENFs groups.<sup>[15,16]</sup>

ALB catabolism and the rate of escape from the intravascular compartment are directly related to the CRP, while the rate of synthesis of ALB is inversely related to the CRP.<sup>[17-20]</sup> Because the % $\Delta$ CRP and the total, non-nutritional, and nutritional calories (TCR, NNC, and NC) were insignificant different among the three ENFs groups, The significant higher % $\Delta$ ALB and significant lower % $\Delta$ CRP:ALB in Group II cohort compared with Group I cohort may be explained by the significant higher %PC<sub>TC</sub> and PD in studied hypoalbumemic patients on RenaMent<sup>®</sup> compared with studied hypoalbumemic patients on either Ensure<sup>®</sup> or Resource<sup>®</sup>Optimum (18.78%±1.43% vs 15.11%±1.42% or 15.92%±1.27% and 4.68±0.67 g/100 Cal vs 3.77±0.74 g/100 Cal or 3.98±0.76 g/100 Cal, respectively). In addition to aforementioned explanation, RenaMent<sup>®</sup> protein profile is totally from whey protein (WP) in contrast to other two tested ENFs which are composed of mixture from WP, casein protein (CP), and soy protein (SP). WP is well documented as high biological value (BV) protein and has the highest BV in compared to CP and SP with BVs of 1, 0.8, and 0.76, respectively.<sup>[21-24]</sup> The high protein BV of RenaMent<sup>®</sup> may also explain the significant higher differences of % $\Delta$ ALB and % $\Delta$ BW when compared with other standard ENFs. Ultimately, if we conserve ALB and LBM from catabolism as possible, the consequences of morbidities and mortalities are expected to be lower and this correlation may explain the lower overall 28-day hospital mortality and overall hospital LOS in Group II compared with Group I.<sup>[25-28]</sup>



**Fig 1. Flow chart of critically ill patient's selection and data collection process.**

Apr: April. CRP: C-reactive protein. CRP:ALB: CRP to ALB ratio.  
 Mar: March. LOS: Length of stay ALB: Albumin.  
 N: Number of studied patients. CER: Cost-effectiveness ratio. H.ALB: g Human Albumin used.

**Table 1 Comparison data between Standard ENFs (Ensure®, Resource®Optimum) and RenaMent®.**

Variables	Total(N=326)	Standard ENFs			P-Value	
		Ensure®(N=109)	Resource® Opt (N=106)	Specialized ENFs RenaMent® (N=111)		
Age (Yrs)	58.37±9.95	59.58±10.37	57.93±9.79	57.59±9.64	0.003(S)	
Gender	Male	224 (68.7%)	70 (64.2%)	75 (70.8%)	79 (71.2%)	0.463(NS)
	Female	102 (31.3%)	39 (35.8%)	31 (29.2%)	32 (28.8%)	
Ward	Non Critical unit	159 (48.77%)	53 (48.62%)	52 (49.06%)	54 (48.65%)	0.312 (NS)
	Critical unit	167 (51.23%)	56 (51.38%)	54 (50.94%)	57 (51.35%)	
Medical Dx	Medical	162 (49.69%)	55 (50.46%)	51 (48.11%)	56 (50.45%)	0.556 (NS)
	Surgical	164 (50.31%)	54 (49.54%)	55 (51.89%)	55 (49.55%)	
BW <sub>1</sub> (Kg)	74.17±10.23	75.04±9.37	73.01±10.59	74.41±10.66	0.316(NS)	
	BW <sub>2</sub> (Kg)	76.44±12.64	76.88±11.91	75.21±14.23	77.23±11.78	0.144(NS)
%ΔBW	3.06%±13.12%	2.45%±13.55%	3.01%±14.37%	3.79%±11.51%	0.031 (S)	
ODs	Worsening	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.000 (S)
	Insignificant improved	86 (26.4%)	72 (65.5%)	10 (9.3%)	4 (3.7%)	
	Slightly improved	132 (40.5%)	30 (27.3%)	96 (88.9%)	6 (5.6%)	
	Moderately improved	102 (31.3%)	8 (7.3%)	2 (1.9%)	92 (85.2%)	
	Greatly improved	6 (1.8%)	0 (0.0%)	0 (0.0%)	6 (5.6%)	
CRP <sub>1</sub> (mg/dl)	7.94±3.11	7.74±2.97	7.85±2.91	8.23±3.42	0.110(NS)	
ALB <sub>1</sub> (g/dl)	2.75±0.32	2.77±0.32	2.74±0.27	2.74±0.37	0.537(NS)	
H.ALB <sub>1</sub> (g/day)	16.99±5.10	16.88±5.04	1736±4.64	16.6±5.59	0.937(NS)	
CRP: ALB Ratio, (X: 1)	3.04±1.49	2.94±1.42	2.99±1.41	3.19±1.64	0.083(NS)	
CRP <sub>2</sub> (mg/dl)	34.16±17.91	34.59±18.93	33.74±16.73	34.12±18.12	0.182(NS)	
ALB <sub>2</sub> (g/dl)	3.54±0.49	3.29±0.39	3.35±0.31	3.98±0.42	0.000(S)	
H.ALB <sub>2</sub> (g/day)	5.83±5.41	8.73±5.09	7.96±4.05	0.74±2.63	0.000(S)	
CRP: ALB Ratio, (X: 1)	9.96±5.79	11.46±7.06	9.68±4.82	8.71±4.90	0.002(S)	
ΔALB (g/dl)	+0.79±0.39	+0.55±0.23	+0.57±0.12	+1.25±0.25	0.000(S)	
ΔH.ALB (g/day)	-11.17±6.01	-8.36±4.98	-8.89±3.16	-16.29±5.89	0.000(S)	
%Δ ALB	29.18%±15.01%	20.11%±8.56%	20.91%±4.71%	46.67%±11.19%	0.000(S)	
%Δ CRP	386.8%±366.3%	398.5%±307.8%	389.5%±337.8%	372.2%±443.3%	0.865(NS)	
%Δ CRP:ALB ratio	285.1%±300.4%	318.5%±267.2%	307.2%±289.5%	228.9%±335.8%	0.057(NS)	
ENF Vol (ml/day)	845.52±343.54	980.13±362.08	979.02±279.44	574.93±190.54	0.000(S)	
# Feeding (#/day)	5.84±1.46	5.75±1.44	5.90±1.47	5.87±1.47	0.072(NS)	
Feeding vol (ml/day)	153.72±75.04	184.18±76.08	176.70±74.28	99.70±35.45	0.000(S)	
Tolerance	GI Sx (0,1)	178 (54.6%)	42 (38.5%)	59 (55.7%)	77 (69.4%)	0.000(S)
	GI Sx (≥2)	148 (45.4%)	67 (61.5%)	47 (44.3%)	34 (30.6%)	
GRV(ml)	152.61±14.07	155.91±13.49	151.78±11.64	150.15±16.09	0.082(NS)	
Non Pro-Kinetics	Erythromycin	135 (41.41%)	36 (33.03%)	40 (37.74%)	59 (53.15%)	0.000(S)
	Metoclopramide	109 (33.44%)	42(38.53%)	39 (36.79%)	28 (25.23%)	
Pro-Kinetics	82 (25.15%)	31 (28.44%)	27 (25.47%)	24 (21.62%)		

Data are presented as Mean±SD and are analyzed by using ANOVA test or presented as number (Percentage) and are analyzed by using Chi square analysis (at p-value< 0.05).

Yrs: Years. CRP: C-reactive protein H.ALB: Human albumin  
 BW: Actual body weight at admission. CRP: ALB: C-reactive protein to albumin ratio N: Number of study's hospitalized patients.  
 GRV: Gastric residual volume. ENFs: Enteral nutritional formulas ALB: Albumin level  
 1: baseline at admission. GI: Gastrointestinal. S: Significant (P-Value <0.05)  
 2: 2 weeks after admission. Sx: Symptoms. NS: Non-significant (P-Value >0.05).  
 Δ: Changes. ODS: Oedematous status.

**Table 2** Other Comparison data between Standard ENFs (Ensure®, Resource®Optimum) and RenaMent®

Variables	Total(N=326)	Standard ENFs		Specialized ENFs	P-Value
		Ensure®(N=109)	Resource® Opt (N=106)	RenaMent® (N=111)	
ENF Cost (US \$/day)	9.99±6.19	6.82±3.14	6.19±1.83	17.03±5.30	0.000(S)
ENF Cost (USD/ 1g PRO/100 Cal)	2.77 ±1.79	1.84±.96	1.72±0.52	4.77±1.59	0.000(S)
CER (USD/ 1 g ALB/dl)	40.73±32.07	60.73±32.14	47.86±25.31	13.23±14.33	0.000(S)
TC (Cal/day)	1402.6±273.8	1372.2±298.8	1428.6±262.9	1406.7±257.3	0.456(NS)
NC (Cal/day)	1033.3±285.6	1003.9±315.2	1057.9±267.9	1038.7±271.1	0.486(NS)
% NC_TC	72.72%±8.60%	71.88%±9.37%	73.29%±7.94%	73.01%±8.44%	0.205(NS)
NNC (Cal/day)	368.95±96.15	368.21±95.05	370.70±94.72	367.99±99.38	0.294(NS)
% NNC_TC	27.28%±8.60%	28.12%±9.37%	26.71%±7.94%	26.99%±8.44%	0.205(NS)
% PC_TC	16.58%±1.59%	15.11%±1.42%	15.92%±1.27%	18.78%±1.43%	0.000(S)
PD (g/100Cal/day)	4.14±0.72	3.77±0.74	3.98±0.76	4.68±0.67	0.022(S)
% Carb Cal_TC	55.97%±5.53%	60.45%±4.38%	54.81%±4.17%	52.59%±4.74%	0.000(S)
% Lipid Cal_TC	29.52%±4.91%	25.35%±3.21%	28.81%±2.47%	34.49%±3.64%	0.000(S)
g Carb: g Lipid Ratio (X: 1)	2.87±0.78	3.76±0.50	2.68±0.36	2.16±0.28	0.000(S)
RQ	0.84±0.03	0.90±0.03	0.82±0.03	0.96±0.03	0.000(S)
Diarrhea					
No (<3 loose stool/day)	210 (64.4%)	71 (65.1%)	66 (62.3%)	73 (65.8%)	
Yes (≥3 loose stool/day)	116 (35.6%)	38 (34.9%)	40 (37.7%)	38 (34.2%)	0.849 (NS)
Overall ENF days	17.65±2.19	17.78±2.44	18.06±1.98	17.1±2.14	0.099 (NS)
Overall Hospital LOS	14.24±6.83	15.08±7.02	14.40±6.88	13.26±6.53	0.007(S)
Overall 28-day Survival	218 (66.9%)	66 (60.6%)	69 (65.1%)	83 (74.8%)	
Overall 28-day Mortality	108 (33.1%)	43 (39.4%)	37 (34.9%)	28 (25.2%)	0.073 (NS)

Data are presented as Mean±SD and are analyzed by using ANOVA test or presented as number (Percentage) and are analyzed by using Chi square analysis (at p-value< 0.05).

ENFs: Enteral nutritional formulas  
 CER: Cost-effectiveness ratio.  
 TC: Total calories.  
 RQ: Respiratory quotient.  
 H.ALB: Human albumin.  
 LOS: Length of stay day(s)

S: Significant (P-Value <0.05).  
 NS: Non-significant (P-Value >0.05).  
 N: Number of study's hospitalized patients.  
 ALB: Albumin level.  
 Carb: Carbohydrates.  
 Cal: Calories.

NC: Nutritional calories.  
 NNC: Non nutritional calories.  
 PRO: Protein.  
 PC: Protein Cal.  
 PD: Protein density.

In summary, most standard ENFs have a PD lower than 4 g/100 Cal and CD lower than 1.2 Cal/ml which increases the risk of overfeeding, feeding intolerance, and fluid overload. So, using specialized ENFs with high CD (>1.5 Cal/ml) and at least moderate PD (4-4.9 g/100 Cal) may have an overall positive clinical and economic impacts in malnourished hypoalbumenic hospitalized patients.<sup>[29-32]</sup> This study is limited by its retrospective design and the use of single-centre data. 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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