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Research Article

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What do we know about covid-19 critically ill patients receiving enteral nutrition? a cross-sectional study

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Abstract

Background and Aims: *Given the need to nourish critically ill COVID-19 patients, whose specific issues may hinder their nutritional supply, this research aimed to evaluate individuals who fed enteral nutrition (EN) and compare them with patients fed orally (ON), in order to assess their profile and find significant differences between both groups.*

Methods: *This is a cross-sectional study in which demographic, medical and laboratory data of EN and ON severe patients with COVID-19 were collected from electronic medical records. Univariate and multivariate analysis inferred and confirmed Prevalence Ratio (PR) of these variables, respectively.*

Results: *A total of 211 medical records were assessed (EN=123). EN patients were mostly male, over 50 years old, overweight or obese, using invasive mechanical ventilation (IMV) and vasopressor drugs (VD). They presented high levels of SAP3 (Simplified Acute Physiology Score 3), d-dimer and brain natriuretic peptide (BNP), as well as low lymphocyte counts. Death rate was 44,71%. In significant comparisons between EN and ON groups, IMV (PR=7.06, p<0.001), hemodialysis (PR=1.57, p<0.001), VD (PR=2. 16, p<0.001), CT lung injury>50% (PR=1. 31, p=0.039), high BNP (p=0.001) and SAPS3 (p<0.001), lymphopenia (p<0.001) and death (PR=2. 19, p<0.001) prevailed in the former. Logistic regression supported statistical significance for IMV (z=7.027, p<0.001), VD (z=3.473, p=0.001), low lymphocytes count (z=-3.785, p=0.001), and death (z=2.692 and p=0.007).*

Conclusion: *1) EN patients were more severely ill than those ON. 2) When correlated with ON, EN group had higher rates of IMV, VD, lymphopenia and death.*

Background

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes COVID-19, a disease whose severe manifestation can transfer patients to the intensive care unit (ICU), which in itself is a risk factor for increasing mortality rates [1,2]. Beyond respiratory system, SARS-CoV-2 invades gastrointestinal tract, since this virus receptor, angiotensin-converting enzyme 2 (ACE2) gene, is also abundantly expressed on digestive cells [1]. This disruption of intestinal mucosa causes symptoms such as diarrhea, vomiting, nausea, anorexia, and may also impact nutrients absorption [3,4].

In combination with effects of respiratory and digestive symptoms on dietary intake, severe COVID-19 promotes hypermetabolism and hyperinflammation, which results in increased protein and micronutrient expenditure [3-6]. Invasive mechanical ventilation (IVM), bed immobility, sedatives, and neuromuscular blockers accentuate an intense loss of muscle mass in these critically ill patients [6-8]. All above impact functional recovery of ICU COVID-19 patients, impair their nutritional requirements (NR) provision, and raise complications such as gastrointestinal hypomotility [8-12]. Furthermore, there are still constraints in NR full assessment because of patient isolation, which restricts ICU teams, use of imaging methods in nutritional diagnosis, and indirect calorimetry [3,12].

Age, diabetes mellitus (DM), hypertension, obesity and multiple comorbidities are the major risks for severe Covid-19 [10,13,14]. Interestingly, as in DM and hypertension, ACE2 can relate to SARS-CoV-2 and obesity. ACE2 receptors are reported in both the type 2 pneumocyte and adipocyte [13].

Nutritional Support (NS) is an important multidisciplinary therapy, which contributes to faster recovery and reduced mortality in ICU subjects [15-18]. COVID-19 pandemic has brought challenges to its proper management, as already mentioned [6]. Oral nutrition (ON) remains first choice for feeding inpatients [7]. Parenteral nutrition is unusual in these cases [7]. However, Enteral Nutrition (EN) is often required [6].

Most COVID-19 ICU patients on invasive MV fed by EN [6,7]. Recommendations for NS in these cases have been published and periodically updated by International Societies, given that acquaintance about SARS-CoV-2 disease is still incomplete [19-23]. Whereas understanding the profile of these severe ill individuals fed by EN may improve strategies for adequate provision of their NR and reduction of NS complications, this study aimed:

- To analyze critically ill patients with COVID-19 using EN in a tertiary care hospital;
- To compare the researched information with those of similar patients fed by ON to lay out specific characteristics of each group in order to adjust NS accordingly.

Method

Research Design

This is an observational, analytical, cross-sectional type study. Data sources were electronic medical records of adult ICU patients with Covid-19 in a tertiary hospital. Findings were collected from hospitalized patients during the period between June 2020 and April 2021 in a partnership with the Federal University Ethics and Research Committees of both institutions approved this survey through CAE 35128820.0.0000.5546.

Patients fed EN were compared with those receiving ON. Medical records on parenteral nutrition and children were excluded. Investigated variables were nutritional route, age, sex, hypertension, DM, obesity, hemodialysis, vasopressor drugs (VD), deep vein thrombosis, invasive mechanical ventilation (IMV), weight, body mass index (BMI), leucocytes and lymphocytes count, hemoglobin (Hb), Creactive protein (CRP), D-dimer, brain natriuretic peptide (BNP), percentage of lung injury on chest CT (%CT), severity score (Simplified Acute Physiology Score III - SAPS3), and mortality.

Statistical analysis

For categorical variables, analyses were conducted using Prevalence Ratio (PR), its confidence intervals, and Chi-square p-value. Since most of numerical variables tended to be asymmetric, the non-parametric Mann Whitney test was used. Logistic regression models were run including all variables with p-value ≤ 0.05. Variables with collinearity risk as well those with missing values>20 % were excluded from the cited models. Significant p value was ≤ 0.05.

Nutritional Support

All evaluated patients were monitored by a multidisciplinary NS team. Covid-19 recommends of the North American (ASPEN) and European (ESPEN) Societies for Parenteral and Enteral Nutrition were followed. Oral nutritional supplementation (ONS) was prescribed when ON patient did not achieve at least 80% of his or her NR. EN was appointed, preferentially by gastric route, in case that a minimum of 60% of the NR were not met by ON. Enteral diets and ONS were mainly polymeric, low osmolar, hypercaloric, and had high protein (20 to 24%). In case of persistent gastroparesis, post-pyloric or jejunal route was chosen. Supplements of hydrolysate proteins, vitamins and microminerals, especially zinc, were routinely provided.

NS was indicated as early as possible, in the first 24 to 48 hours of ICU admission, except in hemodynamic instability or refractory hypoxia. For severely ill Covid-19 patients, a NR of 15-20 kcal/kg/day was initially defined. After their clinical stabilization, NR progressively increased to 25-30 kcal/kg/day. In a recovery phase, generally outside the ICU, a NR of 30-35kcal/kg/day were prescribed. Protein intake was 1.2 to 2.0 g/kg/day.

Current or usual weight was assumed. In obese patients, NR was 11 to 14 kcal/kg/day (current weight) with protein intake up to 2.0 g/kg/day (ideal adjusted weight). Calories from propofol and glucose infusion were added in to NR. Information regarding weight and height of sedate or non-interactive individuals was obtained from their family members. Anthropometry and indirect caloric were performed after end of isolation period.

Results

A total of 211 medical records of ICU patients were accessed, of which 123 received EN. More than 75% of EN subjects were older than 50 years, overweight or obese, and on IMV, had high SAPS 3 score, BNP and D-dimer, in addition to lymphopenia. Further, 57.72% were men, 61.79% were hypertensive, 52.85% used vasopressor drugs, 35.77% had lung injury >50%, and 44.71% died. In contrast, only 5.68% were on IVM, 7.95% received VD, 21.59% had lung injury by CT >50% and 2.27% died in ON group.

A significant comparison between groups showed an increased predominance of IMV, hemodialysis, vasopressor drug, lung injury by CT>50% by CT, and mortality in EN patients, as shown in Table 1. PR for IMV, VD and death are prominent in the referred table. Note that lung injury by CT<25% was more prevalent in ON group.

Table 1: Predicted Prevalence Ratio (PR) of Sex and medical profile of Covid-19 critically ill patients fed Enteral (EN) and Oral Nutrition (ON).

Features		EN		ON		PR	50% Confidence Interval		p-value C
		n	%	n	%		Minimum	Maximum	
Sex	Men	71	34%	51	24%	1.00	0.79	1.25	1.000
	Women	52	25%	37	18%				
Hipertension	Yes	76	36%	47	22%	1.16	0.91	1.47	0.282
	No	47	22%	41	19%				
Diabetes	Yes	44	21%	34	16%	0.95	0.75	1.21	0.779
	No	79	37%	54	26%				
Obesity	Yes	45	21%	24	11%	1.19	0.95	1.49	0.203
	No	78	37%	64	30%				
Hemodialysis	Yes	41	19%	10	5%	1.57	1.28	1.92	<0.001
	No	82	39%	78	37%				
IVM	Yes	110	52%	5	2%	7.06	4.25	11.73	<0.001
	No	13	6%	83	39%				
Deep vein	Yes	17	8%	5	2%	1.38	1.06	1.79	0.093
thrombosis	No	106	50%	83	39%				
Vasopressor	Yes	65	31%	7	3%	2.16	1.75	2.67	<0.001
drug	No	58	27%	81	38%				
Death	Yes	55	26%	2	1%	2.19	1.82	2.63	<0.001
	No	68	32%	86	41%				
CT<25%	Yes	30	14%	38	18%	0.68	0.51	0.91	0.006
	No	93	44%	50	24%				
CT= 25-50%	Yes	49	23%	31	15%	1.08	0.86	1.36	0.591
	No	74	35%	57	27%				
Ct >50%	Yes	44	21%	19	9%	1.31	1.05	1.63	0.039
	No	79	37%	69	33%				

CChi-Square test; CT: Lung injury by chest computed tomography; IMV:Invasive mechanical ventilation; n: Absolute number; %:Relative number (percentage).

EN group showed higher BNP and SAPS3 values, in addition to lower lymphocyte counts, when compared to ON group, as shown in Table 2.

Table 2: Demographics and biomarkers in critically ill patients with Covid-19 on Enteral and Oral Nutrition.

Features	Enteral Nutrition		Oral Nutrition		p-valueM
	Median	IQA	Median	IQA	
Brain Peptide Natriuretic (≤ 300 pg/ml)	975	3,504	280	1,006	0.001
C Reactive Protein (<1.0 mg/dl)	8.4	14.95	7.15	13.1	0.070
Hemoglobin (12.0-18.0 g/dl)	12.3	2.55	11.95	2.75	0.395
White blood cells (4,000-11,000/mm3)	9,750	5,275	8,860	4,877	0.240
Dimer D (≤ 500 ng/Ml)	1,640	2,062.	1,600	1,543	0.617
Lymphocytes (1,200-2,400cell/mm3)	744	616	1,041	731	<0.001
Age (in Years)	66	22	63.5	28.25	0.064
Weight (in Kg)	78	22.5	72	27.75	0.093
BMI (25-29.9 kg/m2 overweight)	28.42	6.37	25.8	9.48	0.495
Simplified Acute Physiology Score 3	59	18.5	51	14.5	<0.001
BMI: Body mass index; IQA:Interquartile amplitude; M:Mann Whitney test; ( ):Normal range.					

Logistic regression confirmed that patients receiving EN had a prevalence ratio of IMV (z-value=7.027, p-value< 0.001) and VD (z-value=3.473, p-value=0.001) significantly higher than those in ON. Similarly, there was a strong statistical significance (z-value= -3.265 and p-value=0.001) for lymphopenia in EN group relative to ON. Table 3 showed these finds below..

Table 3: Logistic regression for variables whose prevalence ratio showed p-value <0.05 in covid-19 critically ill patients fed by Enteral and Oral Nutrition.

	Coefficient	Standard error	z-value	p-value
Intercept	-1.542	0.517	-2.984	0.003
Hemodialysis	1.348	0.760	1.775	0.076
Invasive Mechanical Ventilation	5.236	0.745	7.027	<0.001
Vasoactive drug	2.604	0.750	3.473	0.001
Computed tomography lung injury >50%	0.129	0.682	0.189	0.850
Death	-1.661	1.271	-1.307	0.191
Lymphocytes	-0.001	0.000	-3.265	0.001

In the quoted model, CT lung injury<25% variable was removed due to its collinearity with CT lung injury>50% one. BNP and SAPS3 variables were also excluded because they had a missing value rate higher than 20%. Also concerning collinearity, all deaths happened in IMV individuals and none of those who were not on IMV died. So, IMV and death were collinear variables and one had become confounding of the other. Therefore, a new logistic regression was performed, except for the IVM variable. Table 4 illustrated this new model, in which death showed significant results (z-value =2.695 and p-value<0.007), as did lymphocyte count (z-value =-3.785 and p<0.001).

Table 4: Logistic regression for variables whose prevalence ratio showed p-value <0.05, except for invasive mechanical ventilation, in covid-19 critically ill patients fed by Enteral and Oral Nutrition.

	Coefficient	Standard error	z-value	p-value
Intercept	0.598	0.334	1.788	0.074
Hemodialysis	0.941	0.485	1.942	0.052
Vasoactive drug	1.241	0.638	1.945	0.052
Computed tomography lung injury>50%	0.192	0.404	0.476	0.634
Death	2.969	1.102	2.695	0.007
Lymphocytes	-0.001	0.000	-3.785	0.001

Figure 1 demonstrated a high prevalence of lymphopenia in surveyed groups, especially in EN, whose 3rd quartile still had a low lymphocyte count value (normal rate>1,200 cell/mm3).

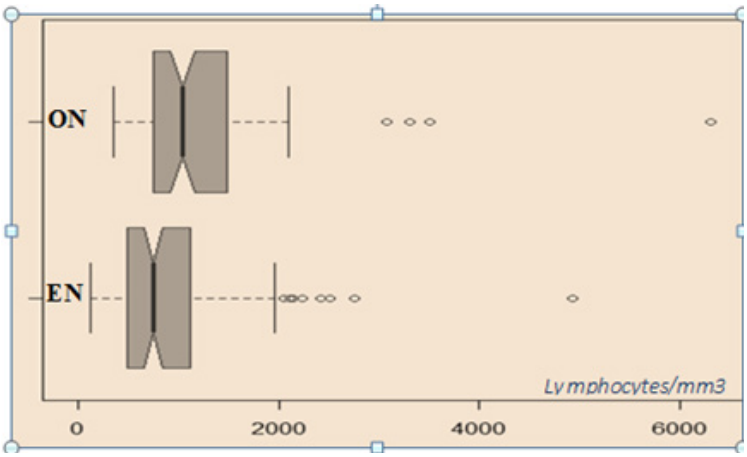

Figure 1: Boxplot graph: lymphocyte distribution in COVID-19 critically ill patients receiving Enteral (EN) and Oral Nutrition (ON). Normal ratio>1,200 cell/mm3.

Dicussion

In the assessed EN Covid-19 ICU patients, we observed significant p-values for PR of increased severity indicators, including IMV, vasopressor drugs, hemodialysis, lung injury>50% on CT scan, severity score (SAPS 3), BNP, lymphopenia, and death. On other hand, individuals feeding by ON showed significant p values for CT lung lesions <25%.

Unexpected, there was no significant age difference between the groups, unlike results of another research from the same hospital, in which we compared zinc levels in EN and ON critically ill patients before COVID-19 pandemic [24]. There was no mortality difference between EN and ON subjects in the referred paper, but there was a mean age over 75 years, in both groups and, even so, age was significantly higher in EN patients [24]. In a recent systematic literature review, Lim et al. reported that case fatality rates among adults with COVID-19 receiving IMV was higher in older patients [25].

In critically ill patient, IMV may negatively impact EN administration due to sedatives prescription and gastroparesis and digestive side effects rates [26]. Nevertheless, early enteral diet reduces infections, IMV and ICU time, and mortality, while accelerating recovery and discharge in this population [26,27]. Therefore, NSTs must address the challenge of nourishing COVID-19 severely ill patients despite the increased potential for complications and dietary intolerance added by this viral. So, we kept in our results the logistic regression with or without IVM, since the other collinear variable (death) was an essential outcome parameter and Covid-19 mortality is linked to ARDS [28].

There are many controversies about EN in critically ill patients using vasopressor, especially about a safe dose for beginning therapy. Despite the drug doses, clinical signs are still the most important parameters in the evaluation of EN tolerance [27, 29]. As expected, in our sample, EN individuals presented a higher rate of vasopressor drug prescription.

Lung injury by CT may be associated to COVID-19 severity and blood level of circulating cytokines [30,31]. Not surprisingly, the highest rate of lung injury >50% happened in the EN group. Although some authors do not associate high admission SAPS 3 score with death rate in COVID-19 ICUs [32], a recent study correlated this with 90-day mortality [33]. High BNP levels also were relative to fatality rate in critically ill COVID-19 subjects [34,35].

Acute kidney injury (AKI), frequent among critically ill COVID-19 patients, may require renal replacement therapy (RRT). Moreover, it is an indicator of disease severity and a poor prognostic factor [14,36]. Pathophysiology of AKI is multifactorial, not only associated with systemic factors, but with direct viral effect on glomerular cells via ACE2 receptors, in conjunction with endothelial dysfunction, coagulopathy and complement activation [14,36]. Again, it is no wonder that EN patients have a stronger request for hemodialysis than those fed orally. Remarkably, lymphopenia on hospitalization is also a risk factor for AKI [14].

Diet and nutritional status impact virtually every aspect of body physiology and are major regulators of T-cell biology, memory, and host fitness in the face of organic stress [37]. Lymphopenia or a high Neutrophil/ Lymphocyte ratio can be mortality indicator in surgery [38], chronic diseases [39], cancer [40], and in critically ill patients, including septic [27] and COVD-19 individuals [32-35]. Severe COVID-19 patients, in comparison with moderate ones, displayed expressively reduced CD4+ T-cell, CD8+ T-cell, B-cell, NK-cell and total lymphocyte counts [41]. Our results showed a normal lymphocyte count in less than 25% of subjects with severe COVI-19 fed on EN, a correlation that reflects not only severity, but also an urgent demand for nutritional support in such patients. This insight reminds ICU teams of the relevance of early and adequate EN, including macro (protein in emphasis) and micronutrients [42]. The best possible strategies to achieve such goal may comprise a Multidisciplinary NST action with strict control of complications, EN administration by infusion pump, changes in diet formulations and access routes, and even supplemental parenteral nutrition, if demanded.

A limitation of the present research is the n, which was higher would, perhaps, allow for statistical significance in correlations with other variables (e.g., age and hemodialysis). Another bound to note is survey design, only enabled PR, not Odes Ratio or Risk Ratio. Nonetheless, conducting clinical trials or case-control studies in unusual conditions arising from COVID-19 pandemic, may be impossible or carry serious ethical implications.

Conclusion

- The assessed COVID-19 critically ill patients fed Enteral Nutrition (EN) were predominantly male, aged over 50 years old, hypertensive, with SAPS 3 severity score>50, on invasive mechanical ventilation and vasopressor drugs, and presented lymphopenia. More than 1/3 of these individuals died.
- When compared to those on Oral Nutrition (ON), EN subjects were more severely ill. They had significantly higher SAPS3 score, higher brain natriuretic peptide, higher percentage of CT lung injury, more frequent invasive mechanical ventilation and hemodialysis, as well as vasopressor drugs and death. Lymphocyte count was also lower in the EN group.
- Prevalence Ratio was statistically significant for invasive mechanical ventilation, vasopressor drug use, mortality and lymphopenia for EN subjects relative to those in ON.
- Despite hardships, Nutritional Support is essential in critically ill patients with COVID19.

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