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## Original article

# Effect of parenteral nutrition in oxygen escalation/de-escalation in SARS-CoV-2 infected patients who are pre-intubation: A multicenter, observational study



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## SUMMARY

**Background & aims:** SARS-CoV-2 infection includes a variety of gastrointestinal manifestations along with the usual viral symptoms of malaise and myalgias. The objective of this study was to determine if intravenous parenteral nutrition (PN) affected the risk of intubation in SARS-CoV-2 patients who were dependent on non-invasive ventilation.

**Methods:** Retrospective, multicenter case-control study which analyzed oxygen requirements for 1974 adults with SARS-CoV-2, who were admitted to the local public hospital system between March 1 and May 17, 2020. Relevant baseline biomarkers were studied over 5 days. The main outcome was an escalation or de-escalation of oxygen requirements relative to the exposure of PN.

**Results:** 111 patients received PN while on non-invasive ventilation. Patients who received PN had a significantly lower odds ( $p < 0.001$ ) of oxygen escalation in comparison to their control group counterparts (OR = 0.804, 95% CI 0.720, 0.899) when matched for age, body mass index, Charlson comorbidity index, and gender.

**Conclusion:** Initiating PN in the setting of non-invasive ventilation of SARS-CoV-2 infected patients was significantly associated with a lower odds of oxygen escalation. PN does not independently exacerbate oxygen requirements in SARS-CoV-2 infected pre-intubated patients.

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## 1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), or Coronavirus 2019 (COVID19), is a novel coronavirus, the symptoms of which generally include diarrhea, loss of appetite, loss of taste and smell, dyspnea, and increased supplemental oxygen

requirements, along with the usual viral symptoms of malaise and myalgias [1,2]. Given the potential extensive nature of gastrointestinal manifestations of this viral syndrome, it became imperative to further analyze the role nutrition may play in the progression of the disease state. In addition to older age, comorbidities including diabetes, hypertension, and obesity were associated with poorer prognosis [3]. The severity of gastrointestinal symptoms in conjunction with the nutritional status of the patient may provide an explanation on the extent of clinical manifestations in a demographic population which was otherwise not considered vulnerable to the virus.

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In a retrospective review from Korea of 198 patients who presented with community acquired pneumonia, 39.4% of the patients met the criteria for malnutrition, such that the elderly population had an almost 5-times greater prevalence of malnutrition than younger patients [4]. The researchers also demonstrated that malnutrition was associated with a higher risk of 2-year mortality in these patients, as did the Charlson comorbidity index score. Similarly, Holter et al. [5] correlated low serum albumin levels—a marker corresponding to individual nutritional status—at admission with a higher risk of death, such that risk increased by 25% for every 5 g/L decrease in serum albumin level. In other words, as a negative acute phase reactant, a decrease in serum albumin level was associated with a higher inflammatory state. These findings were recently corroborated in the context of SARS-CoV-2 infection when severe clinical courses were associated with poorer prognosis [6]. Although recommendations had been proposed to enhance enteral feeds in SARS-CoV-2 patients and monitor nutrition status [6,7], there had not been a study investigating the role of nutrition in patients who cannot tolerate oral intake. There was no standard guideline established for the administration of intravenous parenteral nutrition (PN) and was extremely subjective per the providing care team.

While on non-invasive ventilation such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), patients found it extremely difficult to eat as they would substantially desaturate with temporary reduction or withdrawal of supplemental oxygen. During the early days of the pandemic, high flow nasal cannula was avoided in fear of aerosolization. Trying to ensure both adequate nutrition and oxygenation was complicated by the observation that nasogastric (NG) or orogastric (OG) tube placement prevented a tight seal along the CPAP/BiPAP mask. Moreover, placing a patient with an NG or OG tube in prone position to improve oxygen saturation, increased the risk of aspiration and thus the potential for an even more complicated clinical course ([8–10]). As the placement of a feeding tube was also considered an “aerosol-generating procedure,” PN was viewed as an acceptable alternative [11]. Recently, studies have remarked on the need to address nutrition in the management of SARS-CoV-2 [12], with recommendations that parenteral nutrition should be considered when enteral nutrition is not practical or feasible [13]. Based on the hypothesis that worsening weakness secondary to decreased oral intake contributed to worsening clinical course, the present study endeavored to evaluate whether PN affected the risk of intubation in SARS-CoV-2 infected patients who were dependent on non-invasive ventilation, specifically CPAP or BiPAP.

## 2. Methods

### 2.1. Study design

This was a retrospective, multicenter case-control study analyzing oxygen requirements for 1974 adults admitted to the local public hospital system consisting of 11 hospitals between March 1 and May 17, 2020. The protocol was approved by the Biomedical Research Alliance of New York (BRANY) via the NYCHHC institutional review board and sponsored by NYCHHC's Office of Population Health.

### 2.2. Participants

Patients who were over the age of 18, were not hospice candidates, and required the assistance of either CPAP or BiPAP were included in this study. Pediatric patients and terminally ill patients were excluded. Patients were matched based on gender, BMI, age

and Charlson Comorbidity Index, such that for every patient in the PN group, there were two matched patient in the control group.

### 2.3. Variables

Patients who were included in the subject group were those who received PN, such that they were first introduced while requiring non-invasive ventilation for oxygen. The control group met the same inclusion and exclusion criteria, but did not receive any form of IV nutrition. Variables extracted include patient gender, age, Charlson Comorbidity Index, body mass index (BMI), number of days receiving PN, and morning SARS-CoV-2 and infection/inflammatory laboratory markers for five days since the start of the PN for the PN cohort or the first day of CPAP/BiPAP for the control group.

### 2.4. Data sources

Serologies over five days were selected and were based on the findings of van Mourik et al. [14], who showed that the cumulative fluid balance at 7 days was predictive of mortality in ARDS and not markedly different from cumulative fluid balance at 5 days. Additionally, the average duration of NIPPV usage in a small cohort of patients with acute respiratory failure from severe acute respiratory syndrome was 84.3 h [15]. For the control group, Day 0 was defined as the day of initiation on CPAP/BiPAP. The extracted data was de-identified. Charlson Comorbidity Index was calculated using ICD10 codes and the comorbidity R package [16].

### 2.5. Bias

To reduce the effect of confounders, patients were matched based on age, BMI, gender and Charlson Comorbidity Index between the PN group and the control group using propensity score matching.

### 2.6. Study size

A sample size minimum of 95 subjects was calculated based on a 95% confidence level, a confidence interval of 10, and a potential population size of 10,000. The hospital system data analyst was provided a data collection sheet and a data dictionary to extract data for all SARS-CoV-2 patients who required CPAP/BiPAP and met our inclusion criteria, and were admitted in the hospital system between March 1 and May 17, 2020. This resulted in 111 subjects and 1863 controls.

### 2.7. Quantitative variables

Over the initial five days of PN, oxygen requirement was evaluated as follows: oxygen escalation was defined as a higher oxygen requirement on day 5 relative to day 0, while oxygen de-escalation was defined as a lower oxygen requirement on day 5 relative to day 0. Stable oxygen requirement was defined as no change over the initial five days. Oxygen requirements were assigned a number between –1 and 9 to assist with statistical analysis in the order of escalating oxygen requirements (Table 1). 9 represented death while –1 represented discharge. Day 0 represented the baseline oxygen requirements prior to the first dose of PN. Unless explicitly stated in the EMR flowsheet or affected by an endpoint (discharged or death), missing oxygen requirement data were assumed to be the same as the day before.

**Table 1**  
**Numerical Assignment of Oxygen Requirements.** Oxygen requirements were assigned a number based on the order of escalation to assist with statistical analysis.

Discharged	−1
Room Air	0
Nasal Cannula	1
Simple Mask	2
Non-rebreather/Venturi mask	3
High Flow Nasal Cannula	4
CPAP	5
BiPAP	6
Endotracheal tube	7
Ventilator	8
Death	9

2.8. Patient and public involvement

Not applicable as patients were not directly involved in this study.

2.9. Data sharing statement

No additional data is available.

After grouping the cohorts based on oxygen requirements, day 0 labs were analyzed in an attempt to identify any predictive biomarker. Subsequently, the serology labs were trended over five days following the initiation of PN. The mean for all serological values was calculated for the entire PN and control groups, as well as the subgroups for escalated, de-escalated, or stable oxygen requirements.

2.10. Statistical methods

Multivariate regression models were used to evaluate all covariates using the base R package in R version 1.3.1093 [16]. Odds Ratio were interpreted using the coefficients derived from this model using the KableExtra Package [17]. Patients were matched based on their age, BMI, Charlson Comorbidity Index (CCI), and gender using the MatchIt R package [18] in a 2:1 ratio (2 control patients for every PN patient or 222 controls for 111 subjects) through the nearest neighbor method for propensity score matching. Using a logistic regression model, oxygen requirements over the initial five days while accounting for PN administration were analyzed. A multivariate linear regression model evaluated serologies over the five days.

3. Results

3.1. Participants

111 patients were extracted from the EMR who were on CPAP/BiPAP and received PN.

**Table 2**  
**Patient demographics of the PN and Control Groups.** Patient demographics between the PN cohort and control groups were similar in average age and BMI.

	PN cohort				Control group			
	Total (n = 111)	Stable (n = 34)	Escalation (n = 46)	De-escalation (n = 31)	Total (n = 1863)	Stable (n = 313)	Escalation (n = 554)	De-escalation (n = 996)
Average Age	65	65	64	64	66	65	66	65
Gender								
Male	77	24	34	19	1057	187	352	518
Female	34	10	12	12	806	126	202	478
Average BMI	29	27	30	30	30	31	30	30

The control group consisted of 1863 patients who were on BiPAP/CPAP but did not receive PN.

3.2. Descriptive data

34 patients in the PN group were Female, while 77 were Male. The average age was 65 years and the average number of days on PN was 8 days (Table 2). All PN group patients received IV fluids.

806 patients in the control group were female, while 1057 were male. The average age of this cohort was 66 years. All control group patients received IV Fluids.

3.3. Main result

Patients who received PN had a significantly lower odds (p < 0.001) of oxygen escalation in comparison to their control group counterparts (OR = 0.804, 95% CI 0.720, 0.899) when matched for age, BMI, CCI, and gender.

3.4. Outcome data

In the linear regression model analyzing the serological values, the overall values in serologies was significantly different between the PN group (p = 0.023) when compared to the Control group, such that the PN group had an overall lower odds of increasing inflammatory markers (OR = 0.226, 95% CI 0.063, 0.816). Significant differences where the p-value was less than 0.05 were noted in Day 0 AST (OR 0.992, 95% CI 0.981, 1.003), Day 0 PLT levels (OR 1.009, 95% CI 1.003, 1.015), and Day 1 WBC levels (OR 1.592, 95% CI 1.370, 1.849). Day 0 AST had a confidence interval which crossed 1 and was excluded from the remainder of the analysis. However, univariate analysis evaluating Day 0 PLT and Day 1 WBC was unremarkable.

4. Discussion

Initiating PN in the setting of non-invasive ventilation of SARS-CoV-2 patients was significantly associated with a decrease in oxygen requirements in comparison to the control group. Patients who received PN had significantly lower odds of oxygen escalation than their counterparts who did not receive PN (Odds Ratio <1) when accounted for age, BMI, CCI, and gender. There is a general bias against increasing the fluid volume balance of patients heading towards ARDS, because high volume status has been associated with increased mortality risk [14]. This practice spread to the use of PN in patients who could not tolerate PO intake secondary to the risk of desaturation. Unfortunately, we could not determine if abnormal Cr level was associated to pre- or -post renal etiology or to an AKI from our data. It is important to note that all patients who received PN in this sample did at some point receive IV fluids, however the extent was not quantified and therefore it should not be assumed that any of the patients maintained a euvolemic state.

The importance of monitoring volume status was reiterated in post-intubation septic patients, requiring IV fluids to prevent further end-organ damage [19]. Those who were successfully extubated did receive some level of IV fluids to try to maintain a euvolemic state. These findings are supported by a narrative review which analyzed nutritional risk assessment among multiple studies performed worldwide and determined that critically ill COVID-19 patients are at higher nutritional risk which is associated with poorer clinical outcomes [20].

#### 4.1. Limitations

We were unable to account for other factors or confounding variables that may have impacted the findings, including various other medications or medical interventions. The patients were not followed beyond five days, so little is known about their subsequent clinical courses. Due to the lack of further data, it is unclear how many days the patients were on CPAP/BIPAP prior to being initiating on PN which can also bias the findings. Although a large hospital network was included, only a small number of patients were placed on PN during the study period when the disease was extremely prevalent in New York City. Since patients were placed on PN at the discretion of their providers, the time on treatment varied, as did the amount received. At the time of the study, no protocols existed regarding intravenous nutrition and severe SARS-CoV-2 infection. Another limitation of this study is the inability to evaluate for causes of higher creatinine from the data extraction worksheet, whether it can be attributed to pre- or post-renal causes.

#### 4.2. Conclusion

This study suggests that the maintenance of nutritional and possibly volume status in SARS-CoV-2 patients is associated with a de-escalation of oxygen requirements in pre-intubated patients. Ensuring nutritional needs are met for SARS-CoV-2 infected patients are indicated through IV intake, as it does not exacerbate oxygen requirements. Further studies are needed to better understand the role of intravenous parenteral nutrition with regards to potential benefit and risk in SARS-CoV-2 hospitalized patients. The findings of this study can support the need for monitoring nutrition status for all SARS-CoV-2 infected patients admitted in the hospital.

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#### Authorship and contributorship statement

All authors contributed to the development of this project by engaging in the proposal prior to NYCHHC approval and data extraction, and by contributing to the final analysis and manuscript production.

#### Declaration of competing interest

The authors declare no conflict of interest.

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