Nutritional risk and clinical outcomes in critically ill adult patients with COVID-19

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Introduction: the COVID-19 pandemic put the world’s population at risk. As the relationship between nutritional risk and clinical outcomes in critically ill patients with COVID-19 is still poorly understood, a multidisciplinary research team of the Argentine Society of Intensive Care (SATI) conducted a multicenter study aimed to define nutritional features, and to evaluate the relationship between nutritional risk and relevant clinical outcomes for COVID-19 patients in an intensive care unit (ICU).

Methods: a multicenter, prospective, observational study including twelve Argentinian ICUs was conducted between March and October 2020. Inclusion criteria were: adult patients older than 18 years who were admitted to the ICU with a COVID-19 diagnosis were included. Clinical data included comorbidities scores, and nutritional screening tools such as the Subjective Global Assessment (SGA), the Nutritional Risk Screening (NRS) 2002, and the modified NUTRIC score (mNUTRIC SCORE) were used. In addition, clinical outcomes including overall mortality, mechanical ventilation (MV) days, and ICU and hospital length of stay (LOS) were recorded.

Results: a total of 285 ICU patients met our inclusion criteria. Mean age was 61.24 (SD = 14.6) years; APACHE-II, 14.2 (SD = 6.6); Charlson Comorbidity Index (CCI), 2.3 (SD = 2.3). Most patients were admitted from the emergency room to the ICU. Hypertension, obesity, and diabetes were the most common comorbidities. Nutritional assessment showed that 36.9 % were SGA B+C, and 46 % were obese. Mean ICU LOS was 22.2 (SD = 19.5), and hospital LOS was 28.1 (SD = 21.9) days. Of all patients, 90.2 % underwent MV, and MV days were 20.6 (SD = 15.6). The univariate and multivariate analyses showed that risk factors for COVID-19 mortality were (odds ratio [95 % confidence interval]): SGA score of B or C: 2.13 [1.11-4.06], and NRS 2002 ≥ 3: 2.25 [1.01-5.01].

Conclusions: in the present study, nutritional status (SGA) and NRS 2002 were major mortality risk factors for COIVD-19 patients in the ICU.
INTRODUCTION

The year 2020 began as a very stressful year because of a new potentially fatal disease called COVID-19, caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1), which was primarily detected in Wuhan, Hubei, China. After a brief period, many different retrospective and observational clinical studies were published trying to share some insights into the global pandemic and the infected patients (2). Over the past year, different guidelines and clinical recommendations from international critical care societies for the treatment and management of COVID-19 ICU patients were published (3). However, these international recommendations, aimed to guide healthcare professionals, were mostly based on weak and insufficient evidence (4). Furthermore, nutritional risk screening and early nutritional therapy have been widely recommended for seriously ill patients. So far, however, there is not enough evidence showing a clear relationship between nutritional risk and clinical outcomes.

As a part of the Argentine Society of Intensive Care (SATI), our Metabolic and Nutritional Support Committee (COSONUSME) and the Dietician Section (CALINU) wanted to be prepared when the pandemic arrived in Argentina. That is why we participated in an initiative to collect and translate the information available, and transform it into recommendations for intensive care specialists working in Argentinian ICUs (5).

During this process, our committee acknowledged some inconsistencies in the evidence and lack of information regarding the nutritional characteristics of COVID-19 patients and their relationship with relevant clinical outcomes for the critically ill. As an example of that, according to current evidence there are conflicting data regarding obesity, illness severity, and mortality (6-8).

Most COVID-19 patients who are admitted to the ICU exhibit severe respiratory failure due to isolated viral pneumonia or acute respiratory distress syndrome (ARDS) (8,9). According to current knowledge, there is enough evidence showing a strong association between severe critical illness and malnutrition, muscle wasting, organ dysfunction, and poor clinical outcomes (10). Therefore, nutritional support (NS) and metabolic interventions are a crucial vital support for these patients. Based on these premises, we consider that an adequate assessment of nutritional risk and its relationship with clinical outcomes is necessary (4,6,12) to correctly select the patients who will benefit from NS (9,12).

Therefore, the aims of this study were to define the nutritional characteristics of critically ill patients with COVID-19, and to evaluate any associations between nutritional risk and clinical outcomes in seriously ill adult patients.

METHODS

This is a multicenter, prospective, observational trial that included 12 tertiary-level Argentinian hospitals belonging to the public and private health system.

Inclusion and exclusion criteria were:

- Patients older than 18 years who were admitted to the ICU with a diagnosis of COVID-19 (defined by a nucleic acid-positive nasopharyngeal test + symptoms), requiring MV for more than 48 hours, as well as nutritional support (enteral, parenteral, or both).
- In addition, those patients who received oral nutritional supplements, those with a limitation of care order, and those who refused care at inclusion were excluded.

The approval of each hospital's ethics committee was rapidly granted, and no consent was required due to the observational nature of the trial and the emerging crisis caused by the pandemic.

STATISTICAL ANALYSIS

Continuous data were expressed as mean and standard deviation, while categorical data were expressed as proportions (14). Wilcoxon's rank-sum test (Mann-Whitney U-test) was used for continuous data, and the $\chi^2$ test or Fisher’s exact test for categorical data. Univariate and multivariate analyses were made for mortality (15,16), and all variables with a significant difference were chosen for these tests. We considered a difference to be significant when $\alpha = 5\%$ ($p < 0.05$). The statistical analysis was carried out using the IBM-SPSS® 24 program (15).

RESULTS

In this study, 290 patients were initially recruited. However, 5 were excluded due to unavailable data. In the end, 285 patients (182 and 103 from the private and public healthcare systems, respectively) were finally analyzed (Fig. 1). Table I shows the baseline characteristics of the patient population. A total of 36.9 % were malnourished as defined by the SGA (B and C); mean NRS 2002 score was 3.2 (SD = 1.2), the modified NUTRIC score without Interleukin 6 (mNUTRIC) was 3.5 (SD = 1.8), and 46 % of patients were obese. The most widely used nutritional support form was enteral nutrition (96.84 % of patients). In all, 90.2 % underwent MV, and the mean of MV days was 20.2 (SD = 15.6); 67.2 % were pronated. The length of ICU stay was 22.2 (SD = 19.5) days, and the length of hospital stay was 28.1 (SD = 21.9) days. Finally, 44.9 % of patients died during the study, whereas 41.4 % were discharged, and 13.7 % of patients remained in hospital care.

Chemistry lab results for all patients are listed in Table II; as a significant result, low albumin levels (under 3.5 g/dL) were found in 84.6 % of patients, with a mean of 3.0 g/dL (SD = 0.44).

Table III shows the characteristics of patients who died and survived during the study. Patients who died were older (64.8 (SD, 14.02) vs 58.1 (SD, 14.9) years old, $p < 0.001$); had higher APACHE II scores (15.6 (SD, 6.8) vs 12.7 (SD, 6.1), $p < 0.001$), higher NRS 2002 scores (3.4 (1.1) vs 3 (1.35), $p = 0.0112$), and higher mNUTRIC scores (3.9 (1.9) vs 3.1 (1.7), $p < 0.001$); had more severe malnutrition (SGA C) (46.1 % vs 23.7 %, $p < 0.001$).
and had more comorbidities as measured by CCI (2.5 (SD, 2.3) vs 1.9 (SD, 2.3), p = 0.045). Albumin presented significantly lower levels in the group of patients who died (2.9 (0.42) vs 3.1 (0.46), p = 0.015). These also had less mechanical ventilation (16.6 (SD, 11.6) vs 20.5 (SD, 16.8) days, p = 0.034) and shorter hospital length of stay (21.2 (SD, 21.5) vs 33.4 (SD, 20), p < 0.001). There was no difference in deaths between referring health care systems (private vs public), or when comparing obese vs non-obese patients.

Univariate and multivariate analyses were made for ICU mortality (Table IV). The variables for the analysis were chosen according to the results of the population study (Table III). Patients with APACHE II over 20 were more likely to die during their ICU stay (OR = 2.14; 95% confidence interval (CI) = 1.09 to 4.23; p = 0.027); also patients older than 70 years (OR = 2.29; CI = 1.31 to 4; p = 0.036), patients admitted from the ER (OR = 1.76; CI = 1.00 to 3.09; p = 0.048), patients whose nutritional support was initiated after 48 h (OR = 1.16; CI = 1.04 to 1.3; p = 0.008), and patients with SGA B or C (OR = 2.83; CI = 1.63 to 4.9; p ≤ 0.001), with NRS-2002 of 3 or more (OR = 2.14; CI = 1.15 to 3.99; p = 0.0162), and with a mNUTRIC score of 5 or more (without IL-6) (OR = 1.3; CI = 1.12 to 1.5; p < 0.01). After the multivariate analysis, SGA B or C was an independent factor for dying in the ICU (OR = 2.13; CI = 1.11 to 4.06; p = 0.0221), as was a NRS-2002 of 3 or more (OR = 2.25; CI = 1.01 to 5.01; p = 0.046).

**DISCUSSION**

To our knowledge, this is the first Latin American observational study aiming to evaluate the nutritional status of 285 COVID-19 critically ill patients. The main finding of our study was that malnutrition as assessed with SGA, and risk of malnutrition as assessed with the NRS-2002 are independent factors for in-hospital mortality. Similarly to several other works, we showed that ICU patients with malnutrition have the worst outcome (11,12). Also, sarcopenic patients have the worst outcome in the ICU (13-19). But this work is the first one assessing nutritional risk and malnutrition in COVID-19 patients. The mNUTRIC score was also calculated in this study, and showed significant differences between surviving vs non-surviving patients. These findings, after running the univariate and multivariate analyses, lost their significance.

Another important finding was that the higher the Apache II score (> 20), the higher the mortality among COVID-19 ICU patients, as is observed in non-COVID-19 patients (15-20). Unfortunately, we were unable to determine the SOFA score as a tool to assess organ dysfunction.

Also, CCI was found to be significantly higher in non-surviving patients, meaning that this group of patients had more chronic diseases than surviving patients. In the same way, when comparing comorbidities, we found that non-surviving patients were more likely to have 2 or more comorbidities.
### Table I. Baseline characteristics of the population

| All cases (n = 285) |  |
|---------------------|--|
| **Age (SD), years** | 61.24 (14.6) |
| **APACHE II** | 14.2 (6.6) |
| **Origin** |  |
| Ward | 47.1 % |
| Emergency room | 33.5 % |
| Other center | 19.4 % |
| **Gender (male), n %** | 67.0 % |
| **Charlson Comorbidity Index** | 2.3 (2.3) |
| **Health care system** |  |
| Private | 63.9 % |
| Public | 36.1 % |
| **COPD/asthma** | 10.9 % |
| **Oncologic** | 8.1 % |
| **HBP** | 51.2 % |
| **DM** | 25.3 % |
| **CKD** | 9.1 % |
| **2 comorbidities or more** | 28.4 % |
| **HBP** | 92.4 % |
| **Obesity/overweight** | 84.8 % |
| **DM** | 63.3 % |
| **CKD** | 27.8 % |
| **COPD/asthma** | 25.3 % |
| **Oncologic** | 22.8 % |
| **NRS 2002 (SD)** | 3.2 (1.2) |
| **mNUTRIC score (SD)** | 3.5 (1.8) |
| **SGA** |  |
| ND | 7.4 % |
| Category A | 55.8 % |
| B | 35.8 % |
| C | 1.1 % |
| **Weight, kg** | 89.6 (22.2) |
| **Height, cm** | 169.4 (8.4) |
| **BMI, kg.m⁻²** | 31.2 (7.4) |
| **BMI condition** |  |
| Low weight | - |
| Normal | 13.7 % |
| Overweight | 40.4 % |
| Obese | 46.0 % |
| **MV** | 90.2 % |
| **MV days** | 20.6 (15.6) |
| **Quartile MV days** |  |
| 0-14 days | 44.2 % |
| 15-28 days | 32.5 % |
| 29-42 days | 12.0 % |
| 43 days or more | 11.2 % |
| **Prone** | 67.2 % |
| **Type of NS** |  |
| TPN | 1.85 % (n = 5) |
| CPN + EN | 1.41 % (n = 4) |
| EN | 96.54 % (n = 275) |
| **Time to NS (days)** | 2.58 ± 3.92 |
| **ICU NS days** | 20.11 ± 19.65 |
| **ICU LOS** | 22.2 (19.5) |
| **Hospital LOS** | 28.1 (21.9) |
| **28-day mortality** | 36.5 % |

**Results**
- **Death** | 44.9 %
- **Discharged** | 41.4 %
- **Rehabilitation center** | 3.5 %
- **Continued in ICU** | 10.2 %

### Table II. Lab test results on admission

| n | Mean (SD) |
|---|-----------|
| C-reactive protein (mg/dL) | 90 | 42.6 (70.7) |
| Albumin (g/dL) | 136 | 3.0 (0.44) |
| Albumin < 3.5 g/dL | 136 | 84.6 % |
| Total cholesterol (mg/dL) | 86 | 170.3 (58.3) |
| Triglycerides (mg/dL) | 83 | 237.6 (137.5) |
| AST (U/L) | 184 | 77.9 (297) |
| ALT (U/L) | 184 | 83.9 (139) |
| ALP (alkaline phosphatase) (U/L) | 175 | 144.2 (111.2) |
| Total bilirubin (mg/dL) | 157 | 0.74 (0.76) |
| Conjugated bilirubin (mg/dL) | 127 | 0.55 (0.75) |
| Urea (mg/dL) | 214 | 41.5 (46.5) |
| Creatinine (mg/dL) | 211 | 1.2 (1.04) |
| Plasma phosphorus (mg/dL) | 136 | 3.6 (1.5) |
| Plasma magnesium (mg/dL) | 146 | 2.2 (0.42) |

In our cohort of COVID-19 patients, those who were obese did not show an increased mortality rate in the ICU. As of now, there is conflicting evidence regarding obese patients in the ICU and mortality (21,26). The prevalence of obesity in critically ill patients reported by different cohort studies in Argentina ranges from 10 % to 25 % (27,29). In the present study, the prevalence of obesity is 46 %, indicating that obese patients may be more likely to have a severe form of COVID-19, but we did not find any statistically higher mortality associated with obesity. In a recently published study, obese COVID-19 patients have more commonly fever than non-obese patients, but there were no differences in inflammatory markers, ICU stay, length of mechanical ventilation, or mortality (30). Also, as described by Akinnussi (31), we found that, paradoxically, critically ill obese patients had lower mortality, fewer days in MV, and shorter ICU stay when compared to non-obese patients. In contrast, the meta-analysis made by Jun Yang et al. (7) analyzed 6 retrospective observational studies, only using the BMI tool to determine obesity; however, body composition is perhaps more important than weight and its relation to height squared in determining nutritional risk. None of the published papers described if those COVID-19 obese patients were sarcopenic or not, but this does not prevent meta-analyses on BMI from affirming (32) a relationship between nutritional risk and mortality in association with this poor tool for describing body composition (33,34).

The main laboratory finding in our study was that 84.7 % of COVID-19 patients had low plasma albumin levels (< 3.5 g/dL) (35), and that patients who died had lower levels when compared to those who survived (2.9 (SD = 0.42) vs 3.1 (SD = 0.46), p = 0.015). As we know from previous data related to the critical care general population, albumin is more closely associated with inflamma-
**Table III. Results of the comparison between patients who died and who were discharged**

|                      | Discharged alive (n = 118) | Death (n = 26) | p-value |
|----------------------|----------------------------|----------------|---------|
| Age (SD), years      | 58.1 (14.9)                | 64.8 (14.02)   | < 0.001 |
| APACHE II            | 12.7 (6.1)                 | 15.6 (6.8)     | < 0.001 |
| Origin               |                            |                |         |
| Ward                 | 52.4 %                     | 40.5 %         | 0.061   |
| Emergency room       | 28.2 %                     | 40.5 %         | 0.043   |
| Other center         | 19.4 %                     | 19%            | 0.936   |
| Male                 | 64.4 %                     | 66.4 %         | 0.767   |
| Female               | 35.6 %                     | 33.6 %         | 0.742   |
| Charlson Comorbidity Index | 1.9 (2.3)        | 2.5 (2.3)      | 0.045   |
| Health care system   |                            |                |         |
| Private (n = 150)    | 49.4 %                     | 50.6 %         | 0.64    |
| Public (n = 94)      | 46.2 %                     | 53.2 %         |         |
| COPD/asthma          | 11 %                       | 10.2 %         | 0.831   |
| Oncologic            | 6.8 %                      | 10.2 %         | 0.181   |
| HBP                  | 46.6 %                     | 56.3 %         | 0.129   |
| DM                   | 25.4 %                     | 22.7 %         | 0.621   |
| CKD                  | 6.8 %                      | 11.7 %         | 0.188   |
| 2 comorbidities or more | 35.4 %                 | 49.4 %         | 0.0269  |
| NRS 2002             | 3 (1.35)                   | 3.4 (1.1)      | 0.0112  |
| mNUTRIC score        | 3.1 (1.7)                  | 3.9 (1.9)      | < 0.001 |
| SGA                  |                            |                |         |
| A                    | 9.4 %                      | 6.2            | 0.348   |
| B                    | 66.9 %                     | 47.7 %         | 0.0024  |
| C                    | 23.7 %                     | 46.1 %         | < 0.001 |
| Weight, kg           | 86.6 (16.2)                | 90.2 (25.3)    | 0.182   |
| Height, cm           | 168.7 (7.9)                | 169 (9.1)      | 0.78    |
| BMI, kg.m⁻²          | 30.4 (5.4)                 | 31.3 (8.6)     | 0.33    |
| BMI condition        |                            |                |         |
| Low weight           | -                          | -              |         |
| Normal               | 11.9 %                     | 16.4 %         | 0.314   |
| Overweight           | 44.1 %                     | 39.8 %         | 0.495   |
| Obese                | 44.1 %                     | 43.8 %         | 0.962   |
| Albumin, g/dL        | 3.1 (0.46)                 | 2.9 (0.42)     | 0.015   |
| MV needs (requirement) | 80.5 %                 | 97.7 %         | < 0.001 |
| MV days              | 20.5 (16.8)                | 16.6 (11.6)    | 0.034   |
| Quartile MV days     |                            |                |         |
| 0-14 days            | 46.3                       | 51.6           | 0.407   |
| 15-28 days           | 33.7                       | 34.7           | 0.869   |
| 29-42 days           | 7.4                        | 9.7            | 0.52    |
| 43 days or more      | 12.6                      | 4              | 0.0138  |
| Prone position       | 57.9 %                     | 69.4 %         | 0.061   |
| ICU LOS              | 22.4 (16.8)                | 20.1 (20.7)    | 0.34    |
| Hospital LOS         | 33.4 (20)                  | 21.2 (21.5)    | < 0.001 |

SD: standard deviation; HBP: High blood pressure; DM: diabetes mellitus; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; SGA: subjective global assessment; ND: no data; BMI: body mass index; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit; cm: centimeters; kg: kilograms.

In the present study, critically ill patients with COVID-19 at risk of malnutrition, and those who were malnourished, had a higher mortality rate. Moreover, these patients showed worse outcomes when compared to those who were not at risk or well nourished. Also, obese patients had a higher risk of more severe forms of COVID-19, although obesity was not associated with increased mortality. Finally, the NSR-2002 and the SGA scores were the most accurate tools to establish nutritional risk and status in critically ill patients with COVID-19. Therefore, according to our findings, patients at nutritional risk require an early and adequate nutritional support intervention. Finally, large scale, well designed randomized controlled trials aimed at evaluating nutrition therapy in high-risk patients are warranted.

**CONCLUSION**

The main strength of our study is based on the fact that it was a prospective, multicenter trial focused on nutritional features and relevant clinical outcomes in the critically ill. Moreover, all researchers are ICU physicians and dietitians trained in the nutritional assessment of ICU patients using different tools such as the NRS 2002, SGA, and anthropometric data. Nonetheless, we are aware that our study has several limitations. Ultrasonography or other methods to evaluate muscle mass were not used, and therefore body composition could not be analyzed. Also, caloric and protein intake were not assessed and were not related to clinical outcomes.

**CONFLICT OF INTEREST**

Following our ethical obligation as researchers, we must report that Sebastián Chapela has performed as a speaker for NUTRICIA and FRESENIUS KABI, and participated in Advisory Boards for FRESENIUS-KABI. Andrés Martinuzzo works as Medical Director of NUTRIHOME-SA, and has performed as a speaker for FRESENIUS-KABI Argentina. Claudia Elisabeth Kecskes has performed as speaker for NUTRICIA and FRESENIUS KABI. No potential competing interests were reported by the rest of the authors.
### Table IV. Univariate and multivariate analysis of ICU mortality

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | Odds ratio | 95% CI | p-value | Odds ratio | 95% CI | p-value |
| APACHE II > 20 | 2.14 | 1.09 to 4.23 | 0.027 | 1.44 | 0.59 to 3.54 | 0.42 |
| 70 years or more | 2.29 | 1.31 to 4 | 0.036 | 1.97 | 0.97 to 4.01 | 0.06 |
| Gender male | 1.06 | 0.63 to 1.8 | 0.8 | 0.84 | 0.45 to 1.57 | 0.58 |
| Origin ER | 1.76 | 1.00 to 3.09 | 0.048 | 1.7 | 0.89 to 3.23 | 0.1 |
| Health system | 0.90 | 0.54 to 1.51 | 0.7 | 0.72 | 0.37 to 1.4 | 0.33 |
| Time to initiate nutrition greater than 48 h | 1.16 | 1.04 to 1.3 | 0.008 | 1.11 | 0.59 to 2.09 | 0.74 |
| SGA B or C | 2.83 | 1.63 to 4.9 | < 0.001 | 2.13 | 1.11 to 4.06 | 0.0221 |
| NRS 2002: 3 or more | 2.14 | 1.15 to 3.99 | 0.0162 | 2.25 | 1.01 to 5.01 | 0.046 |
| mNUTRIC score: 5 or more | 1.3 | 1.12 to 1.5 | < 0.001 | 1.15 | 0.38 to 3.44 | 0.79 |
| Obese | 1.05 | 0.63 to 1.74 | 0.85 | 1.38 | 0.76 to 2.53 | 0.29 |
| Diabetes | 1.04 | 0.67 to 1.6 | 0.85 | 0.62 | 0.34 to 1.16 | 0.13 |
| COPD | 0.99 | 0.58 to 1.66 | 0.96 | 0.77 | 0.35 to 1.69 | 0.52 |
| Hypertension | 1 | 0.65 to 1.55 | 0.98 | 1.07 | 0.58 to 1.99 | 0.82 |
| Chronic kidney injury | 0.95 | 0.55 to 1.64 | 0.85 | 1.12 | 0.48 to 2.6 | 0.78 |
| Onologic | 0.79 | 0.46 to 1.36 | 0.39 | 0.94 | 0.39 to 2.23 | 0.89 |

CI: confidence interval; SGA: subjective global assessment; ER: emergency room; COPD: chronic obstructive pulmonary disease.

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