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Nutritional parameters and clinical outcomes of patients admited with COVID-19 in a university hospital

Parâmetros nutricionais e desfechos clínicos de pacientes admitidos com COVID-19 em um hospital universitário

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ABSTRACT

Objective
To evaluate the relationship between nutritional parameters and clinical factors and the outcome of patients diagnosed with COVID-19.

Method
This is a prospective longitudinal study involving patients with COVID-19 infection admitted to a University Hospital in Pernambuco. The sample consisted of individuals aged ≥20 years who tested positive for COVID-19 infection. Nutritional risk was assessed using the recommended screening procedure for this group and the nutritional status using the Body Mass Index. Demographic and clinical variables were transcribed from the medical records.

Results
There was a predominance of adult inpatients between 20 and 59 years of age (95% CI: 64.6-76.0); nutritional risk was observed in 91.6% of patients and overweight in 58.9% of patients. Age ≥60 years (p=0.03), presence of malignancies and inadequate nutrition (p<0.001) were independent risk factors for in-hospital death. It was also observed that only arterial hypertension (OR 2.34, 95% CI 1.32-4.13, p=0.003) and overweight (OR 1.84, 95% CI 1.05-3.21, p=0.032) were considered independent risk factors for admission of the patients in the Intensive Care Unit.

Conclusion
Although overweight is a risk factor for admission in the Intensive Care Unit, it was not possible to observe it as a factor for mortality, requiring further studies to determine the mechanisms that interfere in the association between obesity and mortality in those patients.

Keywords: COVID-19. Nutritional assessment. Nutritional status.

RESUMO

Objetivo

Avaliar a relação dos parâmetros nutricionais e fatores clínicos com o desfecho dos pacientes diagnosticados com COVID-19.

Método

Trata-se de um estudo longitudinal prospectivo envolvendo pacientes com infecção por COVID-19 internados em um Hospital Universitário de Pernambuco. A amostra foi constituída por indivíduos com idade ≥20 anos que tiveram resultado positivo para infecção por COVID-19. O risco nutricional foi avaliado por meio de triagem recomendada para este grupo e o estado nutricional por meio do Índice de Massa Corpórea. As variáveis demográficas e clínicas foram transcritas dos prontuários.

Resultados

Houve predomínio de pacientes adultos entre 20 e 59 anos (95% IC: 64,6-76,0) internados, o risco nutricional foi observado em 91,6% e o excesso de peso em 58,9% dos pacientes. A idade >60 anos (p=0,03), a presença de câncer e aporte nutricional inadequado (p<0,001) foram fatores de risco independente para morte hospitalar. Observou-se também que apenas a hipertensão arterial (OR 2,34, 95% IC 1,32-4,13, p=0,003) e o excesso de peso (OR 1,84, 95% IC 1,05-3,21, p=0,032) foram considerados fatores de risco independentes para a internação do paciente na Unidade de Terapia Intensiva.

Conclusão

Embora o excesso de peso seja um fator de risco para admissão na Unidade de Terapia Intensiva, não foi possível observá-la como um fator para mortalidade, se fazendo necessários estudos para determinar os mecanismos que interferem na associação entre a obesidade e letalidade desses pacientes.

Palavras-chave: *COVID-19. Avaliação nutricional. Estado nutricional.*

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) infection is a disease caused by a betacoronavirus, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); this virus can spread through the air, contaminated surfaces and hands or through direct contact of people through droplets expelled by coughing, saliva, sneezing and body secretions [1].

This new disease can manifest itself as an asymptomatic infection; however there are cases with mild symptoms, such as: anosmia, ageusia, fever, body pain, diarrhea, vomiting, abdominal pain and reduced appetite [2,3]. In more severe cases, the patient may evolve with an exacerbated inflammatory response, with high inflammatory markers that can culminate in SARS, with possible excessive activation of the coagulation cascade [3,4].

There are different risk factors that increase COVID-19 mortality, one of the main ones being age, since elderly patients are characterized by immunosenescence, which causes a decline in the responsiveness of the immune system, leading to more severe outcome of viral and bacterial infections. In addition older adults patients may be affected by multimorbidities [5]. Regardless of age, there are also comorbidities that are prevalent risk factors in these patients, such as: cardiovascular diseases, diabetes, hypertension, chronic respiratory diseases and immunosuppression [6].

It is evident that non-communicable chronic diseases are associated with the worsening of the condition of COVID-19 patients; however the patient's nutritional status can also affect those patients' clinical outcome [6,7]. Obesity, which is also considered a non-communicable chronic diseases, is an independent risk factor for severe SARS-CoV-2 infection, due to its effects on the lung function, such as decreased respiratory reserve, as well as immune dysregulation and high levels of circulating inflammatory markers [7]. In a pooled analysis it was found that patients who

had a worse prognosis had a higher Body Mass Index (BMI). Some authors have demonstrated a direct relationship between a 1-unit BMI increase and a 12% increase in the risk of developing severe COVID-19 [8].

Due to the need to better understand this new epidemic disease's patients, our study is intended to contribute to the current literature, in addition to understanding the factors related to the unfavorable results of this disease and public health planning, with the objective of evaluating the relationship of nutritional parameters and clinical factors with the outcome of patients diagnosed with COVID-19.

METHODS

This is a prospective longitudinal study involving patients infected with COVID-19 treated at the Hospital das Clínicas of the Federal University of Pernambuco.

The sample obtained by convenience consisted of 250 individuals of both genders aged 20 years or over, admitted to the infectious and parasitic diseases ward during the period from April 2020 to June 2021. All individuals had a confirmed diagnosis of COVID-19 infection by the RT-PCR molecular test using a naso-oropharyngeal secretion swab. Patients who did not have recent weight and/or height data for the nutritional diagnosis were excluded.

For the nutritional risk screening, the criteria used were based on comorbidities related to a worse prognosis, indicators and symptoms associated with malnutrition, proposed by Piovacari et al. [9] which establishes nutritional risk when at least one of the following criteria is present: older adult (≥65 years), adults with BMI <20.0 kg/m^2, patients at high risk of pressure injury or with pressure ulcer, immunosuppressed patients, with inappetence, persistent diarrhea, history of weight loss, chronic obstructive pulmonary disease, asthma, structural pneumopathies, heart diseases, including significant arterial hypertension, insulin-dependent diabetes, renal failure as well as pregnant women.

The nutritional variables considered were BMI, whose classification was established according to the cut-off point proposed by the World Health Organization [10] for adults and Lipschitz [11] for elderly people based on weight and height measured on admission. Type of nutritional therapy (oral, enteral and parenteral), and adequate and inadequate nutritional intake were evaluated from the patient's dietary acceptance until the time-point of the outcome according to established individual goals; dietary inadequacy was set at <50% of the established goal.

Demographic and clinical variables were transcribed from the medical records including: age, gender, presence of comorbidities (systemic arterial hypertension, diabetes mellitus, cancer, among others), length of stay, admission to the Intensive Care Unit (ICU) and clinical outcome (death or discharge) respectively.

Data were tabulated in the Excel 2010 program and the statistical analysis was performed using the IBM©SPSS© (version 25.0). Continuous variables were tested for normality using the Kolmogorov-Smirnov test; variables with non-parametric distribution were described as medians and relevant interquartile ranges.

Proportions were described by approximating the binomial distribution to the normal distribution using a 95% confidence interval. In the statistical inference tests, proportions were compared by Pearson's chi-square test and the Wilcoxon test was used to compare dependent sample medians.

The logistic regression model was used to assess the relationship between ICU stay and clinical and nutritional variables. Initially, the univariate analysis was performed with the purpose of selecting the variables for the composition of the multivariate model. For the selection of those variables, the level of significance expressed by a p value lower than 20% was chosen and for the permanence of the variable in the final model, a p value lower than 5% was adopted.

In the survival analysis, we first interpreted the behavior of the response variable at the end of the time exposure, as follows: (i) for each individual, the survival situation, also called outcome, was characterized and interpreted by the time elapsed between admission and the occurrence of the fatal event; (ii) for each individual, the censorship situation was defined, interpreted when the event of interest (death) had not occurred by the end of the observation period (hospital discharge or patient's transfer to another service during follow-up). On the other hand, the mortality rate was calculated using the ratio between the number of deaths and the population assessed.

The assumptions for applying the Cox regression technique were evaluated. The assumption of proportional hazards was met, indicating that this regression model was suitable for the data in this study. For this purpose, the descriptive graphic method and the Log Rank test ($p \leq 0.05$) were adopted to reject the hypothesis that the risks are equal. The extreme situation of violation of this assumption is characterized by curves that intersect. And, finally, to identify the factors associated with death, the variables that met the aforementioned criteria were selected to integrate the Cox multivariate regression model.

The association between the exposure variables and the clinical outcome (death) was assessed using semi-parametric Cox regression and interpreted using the Hazard Ratio (HR), with a 95% confidence interval (95% CI). A significance level of 5% was used to reject the null hypothesis. This investigation was approved by the Hospital das Clinicas Research Ethics Committee, under number CAAE: 48019321.3.0000.8807.

RESULTS

Most of the sample population consisted of patients aged between 20 and 59 years (95% CI: 64.6-76.0), with a higher percentage of men. The most prevalent comorbidities included hypertension, diabetes mellitus and cancer.

Nutritional risk was observed in 91.6% (95% CI: 88.2-95.0) of patients and excess weight in more than half of the sample. Adequate nutritional support was observed in 85.1% (95% CI: 80.6-89.6) of patients.

It was also found that approximately 33% of patients were referred to the ICU and 8.4% died (Table 1).

Table 1 – Demographic, clinical, and nutritional characteristics of COVID-19 inpatients. Recife (PE) Brazil, 2020-2021.

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Characteristics	n	%	95% CI
Gender			
Male	128	51.2	45.0-57.4
Female	122	48.8	42.6-55.0
Age			
20 to 59 years	175	70.3	64.6-76.0
≥ 60 years	74	29.7	24.0-35.4

Table 1 – Demographic, clinical, and nutritional characteristics of COVID-19 inpatients. Recife (PE) Brazil, 2020-2021.

Characteristics	n	%	95% CI
Comorbidities			
Diabetes mellitus	81	32.5	26.7-38.5
Systemic Arterial Hypertension	148	59.4	53.3-65.5
Chronic Kidney Disease	21	8.4	5.0-11.9
Cancer	36	14.5	10.1-18.8
No comorbidities	25	10.0	6.3-13.8
Body Mass Index upon admission			
Malnutrition	27	9.2	7.0-14.8
Eutrophy	78	31.9	25.7-37.2
Overweight	146	58.9	52.7-65.0
Nutritional Risk			
Yes	229	91.6	88.2-95.0
No	21	8.4	5.0-11.8
Feeding route			
Oral	239	97.2	95.1-99.2
Enteral	11	4.5	1.9-7.0
Parenteral	-	-	–
Adequate nutritional support			
Yes	206	85.1	80.6-89.6
No	36	14.9	10.4-19.4
Clinical outcome			
Release	229	91.6	87.5-94.4
Death	21	8.4	5.5-12.5
ICU admission			
Yes	83	33.3	27.6-39.2
No	167	66.7	60.7-72.3
		Median (IQ)	
Days in intensive care unit		8 (3-15)	

Note: CI: Confidence Interval; IQ: Interquartile range.

As shown in Figure 1, the mortality rate in days until the outcome was higher in those individuals who had inadequate nutritional intake and cancer ($p<0.001$). Patients aged ≥60 years also had significant mortality rates ($p=0.03$).

In the crude analysis, inadequate nutrition indicated a greater chance of hospital death (HR 7.48 [3.00-18.64], $p<0.001$). The variables that remained in the model after the adjusted analysis were: age ≥60 years, cancer and inadequate nutrition independently explain a higher risk of hospital death in patients with COVID-19 (Table 2).

It was also observed that only hypertension and overweight were significantly associated ($p<0.05$) with admission to the ICU (Table 3). In the multivariate analysis adjusted for the presence of hypertension (OR 2.34, 95% CI 1.32-4.13, $p=0.003$) and overweight (OR 1.84, 95% CI 1.05-3.21, $p=0.032$) remained in the model; that is, they were considered independent risk factors for patient hospitalization in the ICU (Table 4).

DISCUSSION

In connection with the pandemic, some measures were introduced in some countries, such as restricting people's movement for several weeks, a measure that had a large impact on mobility, resulting in physical inactivity and increased consumption of delivery fast food.

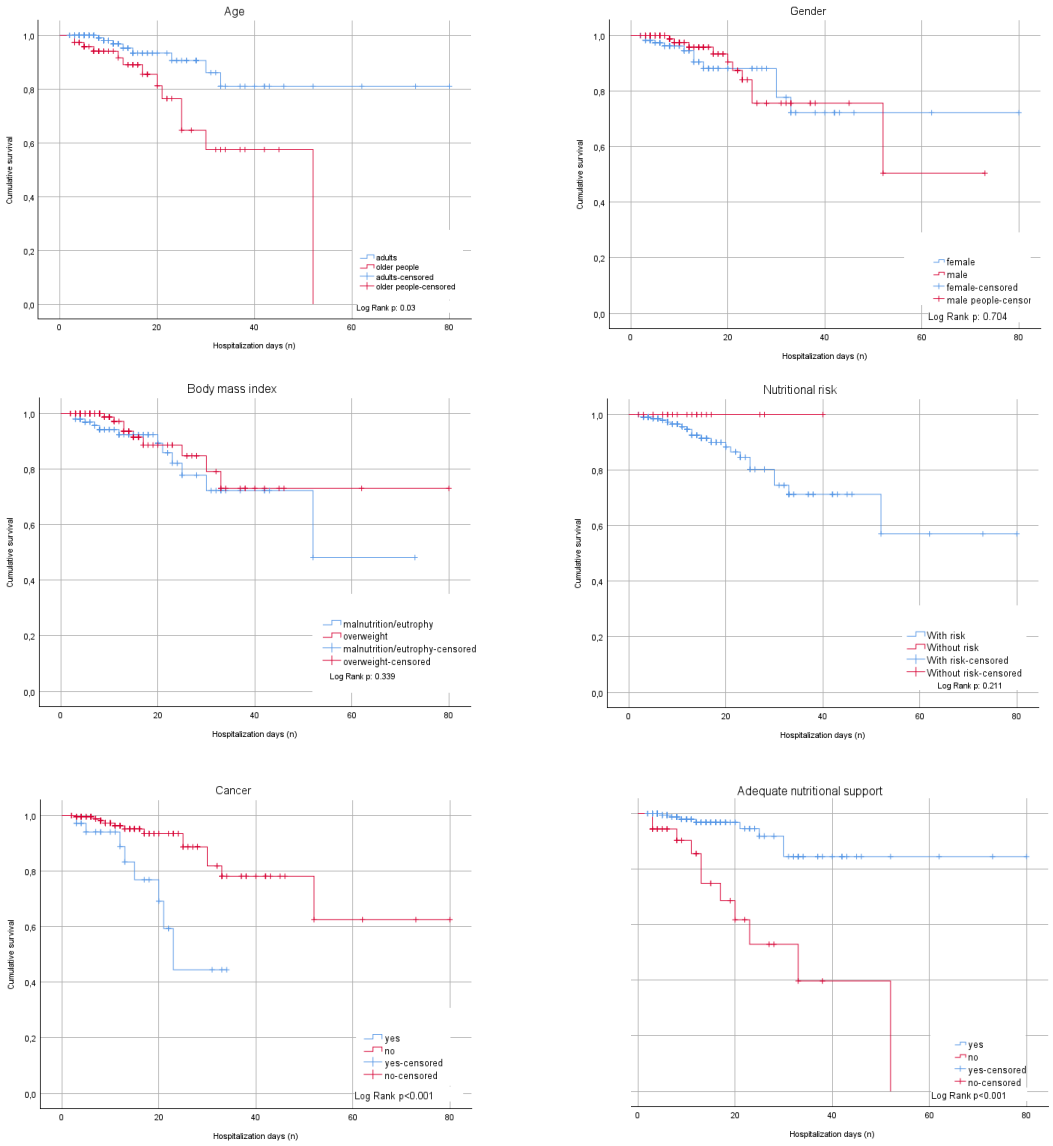

Figure 1 – Kaplan-Meier curves related to death according to age, gender, presence of cancer, adequate nutritional intake, body mass index and nutritional risk in patients with COVID-19. Recife (PE) Brazil.

Table 2 – Crude and adjusted hazard ratio (HR) for death according to demographic, clinical and nutritional variables in patients with COVID-19. Recife (PE) Brazil, 2020-2021.

Variables	Crude analysis			Adjusted analysis		
	Hazard Ratio	95% CI	p^a	Hazard Ratio	95% CI	p^b
Age						
18-59 years	1			1		
≥60 years	3.51	1.45-8.50	0.005	2.64	1.10-7.48	0.032
Cancer						
No	1			1		
Yes	4.43	1.79-10.96	0.001	2.24	1.16-9.04	0.025
Adequate nutritional intake						
Yes	1			1		
No	7.48	3.00-18.64	<0.001	7.09	2.75-18.27	<0.001

Note: [a]Cox regression; [b]Cox regression adjusted for body mass index. CI: confidence interval; HR: hazard ratio.

Table 3 – Association between intensive care unit admission and demographic, clinical and nutritional variables in patients with COVID-19. Recife (PE) Brazil, 2020-2021. (n=83).

Variables	Intensive Care Unit				*p*
	Yes		No		
	n	%	n	%	
Age					
Adult	59	33.9	115	66.1	0.775
Older adults	23	31.1	51	68.9	
Gender					
Female	38	31.4	83	68.6	0.622
Male	45	35.2	83	64.8	
Systemic Arterial Hypertension					
Yes	60	40.8	87	59.2	0.005
No	23	22.8	78	77.2	
Chronic Kidney Disease					
Yes	11	52.4	10	47.6	0.093
No	72	31.7	115	68.3	
Cancer					
Yes	9	25.0	27	75.0	0.330
No	74	34.9	138	65.1	
Nutritional risk					
Yes	76	33.3	152	66.7	1.000
No	7	33.3	14	66.7	
Adequate nutritional intake					
Yes	71	34.5	135	65.5	0.553
No	10	27.8	26	72.2	
Body mass index					
Without overweight	26	25.5	76	74.5	0.043
Overweight	56	38.6	89	61.4	

Note: *Chi-square test.

Table 4 – Crude and adjusted odds ratio (OR) for admission to the Intensive Care Unit according to clinical and nutritional variables in patients with COVID-19. Recife (PE) Brazil, 2020-2021.

Variables	Crude OR			Adjusted OR		
	OR	95% CI	*p	OR	95% CI	*p*
Systemic Arterial Hypertension						
Yes	2.34	1.32-4.13	0.003	1.95	1.08-3.54	0.026
No	1			1		
Chronic Kidney Disease						
Yes	2.37	0.96-5.83	0.061	2.60	1.00-6.77	0.050
No	1			1		
Body mass index						
Overweight	1.84	1.05-3.21	0.032	1.82	1.00-3.31	0.049
Without overweight	1			1		

Note: *Odds ratio. Multivariate logistic regression model: systemic arterial hypertension, chronic kidney disease and body mass index. CI: Confidence Interval.

These restriction periods may increase the risk of metabolic diseases in the future, besides increasing the number of overweight and obese people [12,13]. For World Health Organization, obesity is already considered a worldwide epidemic, and this is mainly associated with the new food profile and sedentary lifestyle [14].

The high prevalence of excess weight observed in hospitalized patients can be explained by the low concentrations of adiponectin (an anti-inflammatory adipokine) and high concentrations of

leptin (a pro-inflammatory adipokine) that negatively affect the immune function; in addition those patients present a reduced respiratory reserve volume, reduced functional capacity and compliance of the respiratory system, as well as a higher expression of the Angiotensin-Converting Enzyme 2 (ACE2), an enzyme used by the SARS-Cov-2 virus to penetrate the lungs, heart and kidney cells, among others [7,15].

In the Cox regression analysis, there was no association between increased mortality and BMI despite the high prevalence of overweight. Therefore BMI is not considered a risk factor for the increased mortality rate in patients with COVID-19. These results corroborate the study by Cummings et al. [16] carried out in New York, in which, although 85% of the population had a BMI >30 kg/m^2, it was not possible to identify it as a risk factor for mortality.

On the other hand, in the logistic regression model, being overweight was a risk factor for ICU admission (1.82 (95% CI 1.00-3.31; p<0.05). Kalligeros et al. [17] demonstrated that severe obesity (BMI ≥35 kg/m^2) is associated with a 6.16-fold risk of ICU admission (OR 6.16; 95% CI: 1.42-26.66). Du et al. [18] in their review study also pointed out that this association remained significant even after adjusting for different variables clinics, which indicates that severe obesity can independently predispose to negative outcomes.

Arterial hypertension can also be considered an independent risk factor for ICU admission, but the mechanisms by which patients with hypertension are more likely to develop severe COVID-19 are not yet well understood [19]. Some studies suggest that the use of ACE inhibitors (ACE) and angiotensin receptor blockers lead to an excess ACE2, causing a worse outcome [17].

In a meta-analysis by Zuin et al. [19], hypertensive patients with COVID-19 had a worse outcome compared to normotensive patients (OR 3.36, 95% CI 1.96-5.74, p<0.0001). Another study carried out in Wuhan, China, showed that hypertension was present in almost half of the patients and was the most common comorbidity. In the univariate analysis, hypertension presented a risk 3.05 times greater (95% CI 1.57-5.92, p=0.001) for hospital death compared to non-hypertensive patients, and this considering it as a risk factor for severe COVID-19 [20].

In our study, age proved to be an independent variable for reduced survival of these patients. Different authors demonstrate that patients aged >60 years had a significantly higher risk of developing severe COVID-19 and death (OR=3.11, 95% CI 1.73-5.61) than those aged ≤60 years (OR=1.77, 95% CI 1.17-2.69) [17]. A possible explanation for this result is that older adults over 60 years of age tend to have multimorbidities, and with advancing age, this combination of different ailments plus immune senescence favors inflammatory processes, increasing susceptibility to different problems including acute infectious diseases causing death [21,22].

Despite the greater vulnerability of these patients, it was not possible to observe an association between older age and the chances of admission to the ICU. In contrast, a study conducted at the university hospital in Wuhan, China, patients requiring ICU care were significantly older, with a mean age of 66 years [IQR, 57-78] vs 51 years of the other patients [IQR, 37-62]; p<0.001 [23].

Another independent risk factor for patient survival is the presence of malignancies, as cancer patients tend to be immunocompromised due to the effects of the antineoplastic therapy in addition to the immunosuppression caused by the disease itself, and may also present with programmed cell death and increased immune response to infection, secondary to the use of immunomodulatory drugs [24]. In addition, individuals with cancer are often older adults aged ≥60 years, with one or more associated comorbidities, putting them at risk with increasing morbidity and mortality in cases of COVID-19 [25]. Finally, these patients, besides being more susceptible to COVID-19 infection

tend to have more frequent contact with the health system for preventive and supportive care, and are thus more exposed to the virus [26].

Liang et al. [27] confirmed these findings using a Cox regression model to assess the time-dependent risks of patients developing serious events and that patients with cancer worsened faster than those without cancer with a mean time of 13 days [IQR 6-15] vs 43 days [20 – not achieved]; $p<0.0001$; risk ratio 3.56 (95% CI 1.65-7.69) after adjusting for age, indicating that patients with cancer may be at greater risk for COVID-19 than individuals without cancer.

Regarding nutritional therapy, most patients received adequate intervention, but it is important to emphasize that those individuals who had an inadequate food intake had a lower survival rate, and this lack of appetite may be associated with symptoms caused by the disease itself, such as ageusia and anosmia, in addition to invasiveness of O^2 therapy [28].

Caccialanza et al. [29], in their multicenter study carried out in 11 Italian hospitals, among the nutritional parameters surveyed, found that only reduced food intake was associated with the risk of death or ICU admission, respectively (HR=3.59 [95% CI 2.01-6.43], $p<0.001$ and HR=2.18 [95% CI 1.47-3.23], $p<0.001$). Likewise, Formisano et al. [30] observed that patients in the infirmary ward who did not reach their nutritional goals had a higher frequency of death compared to those who reached their goals $p\leq0.001$.

CONCLUSION

Although overweight is a risk factor for admission to the ICU, it was not possible to observe it as a factor for increased mortality. Further studies are required to determine the mechanisms that interfere in the association between obesity and mortality in those patients. On the other hand, other important factors were associated with a worse outcome, such as: age, inadequate food intake, cancer and hypertension.

These results underscore the importance of nutritional screening of these most vulnerable patients upon hospital admission, in order to take preventive measures and intervene early. In addition, policies to ensure community access to nutrition and physical activity should be enforced as part of COVID-19 prevention strategies.

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JFS RIBEIRO and IKG ARRUDA contributed to the conceptualization; formal analysis; investigation; methodology; statistical analysis; data discussion. MTO TOMIYA contribuited statistical analysis and ES CASTELLO BRANCO contributed to data collection. LA SOLON e TA DUTRA wrote the manuscript.