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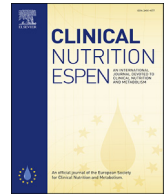
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Original article

Malnutrition risk as a negative prognostic factor in COVID-19 patients

Mancin Stefano ^{a,*}, Bertone Andrea ^a, Cattani Daniela ^b, Morengi Emanuela ^{a,b},
 Passadori Lorena ^a, Donizetti Daniela ^a, Fanny Sökeland ^b, Elena Azzolini ^a,
 Mazzoleni Beatrice ^b

^a IRCCS Humanitas Research Hospital Rozzano, Milan, Italy^b Humanitas University Pieve Emanuele, Milan, Italy

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SUMMARY

Background/objective: SARS CoV-2 infection is a disease, whose prevalence has drastically risen in the past year. The aim of this study is to examine a possible association between the risk of malnutrition, clinical outcomes following hospitalisation and morbidity at discharge.

Methods: This study has analysed the medical records of 652 patients hospitalised at Humanitas Research Hospital (Milan, Italy) between 01/03 and 30/04/2020. The risk of malnutrition was identified with the Malnutrition Universal Screening Tool (MUST).

Results: The cohort was composed of 515 patients. The MUST scale is significantly associated to malnutrition evaluating the morbidity at discharge (discharged 0.27 ± 0.68 , discharged with problems 0.40 ± 0.93 , deceased 0.64 ± 0.93 , $p < 0.001$), and the clinical outcome following hospitalisation (HR 1.25, 95% CI 1.04–1.51, $p = 0.019$) is maintained even after correction for age, treated hypertension, admission to an intensive care unit and oxygen therapy). A subgroup analysis addressing patients with a BMI ≥ 30 shows a significant association between comorbidities such as: arterial hypertension (HR 4.95, 95% CI 1.10–22.22, $p = 0.037$), diabetes (HR 3.37, 95% CI 1.04–10.89, $p = 0.043$) and renal failure (HR 3.94, 95% CI 1.36–11.36, $p = 0.011$).

Conclusions: The results of this study suggest that the risk of malnutrition is a noteworthy indicator that impacts both the clinical outcomes and morbidity at discharge.

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1. Introduction

Infection from SARS-CoV-2 has shown to lead to a condition of extreme clinical severity. Since its first appearance until present no definitive cure has been found, even with ongoing massive research efforts. Many studies have identified risk factors for unfavourable outcome, preventive measures and treatments, to improve the prognostic factors of the disease. Malnutrition has been recognized as one of these factors [1].

Malnutrition is defined as a condition of functional, organic and developmental alteration resulting from an imbalance between required nutrients, actual intake and metabolism leading to an increase in mortality and morbidity affecting life quality. Such a clinical condition can result from reduced intake of macro- and

micronutrients, excessive intake or from an altered nutrient metabolism [2].

Prevalence rates of malnutrition in hospitalised patients in Europe vary according to the criteria used for identification. On average 35% of newly admitted patients (range 10–80%) presents malnutrition, which is generally aggravated during hospitalisation [3].

Malnutrition is the main cause of immunodeficiency in the world, affecting both the innate and the acquired immune response [4], exposing individuals to an elevated risk of infection [5] and a lower capacity to inhibit viral proliferation.

The immune system can further be altered by malnutrition due to excess food intake. Obesity induces a systemic inflammatory state with consequential alteration TCD4 cell response brought about by leptin, increasing autoimmunity [6] along with T-cell exhaustion characterised by reduced effective, proliferative and cytotoxic function [7].

Micronutrient deficiencies are a growing problem in individuals with malnutrition, as vitamins and micronutrients play an important

* Corresponding author.

E-mail address: stefano.mancin@humanitas.it (M. Stefano).

role in allowing correct functioning of the innate and acquired immune response [8–10]. A state of malnutrition associated with a deficit in micronutrients, hypermetabolism and an excessive loss of nitrogen, are all factors known to predispose infection [11].

Furthermore, obesity has a strong link to respiratory diseases. It is widely known to be associated with asthma, obstructive sleep apnoea, acute lung damage and ARDS [12] (acute respiratory distress syndrome). Therefore, the association of severe pulmonary complications from COVID-19 and obesity is now assessed, and obesity is a known risk factor for severe outcome [13–16] also in other form of pandemic influenza like H1N1 [17].

2. Materials and methods

A retrospective cohort study was carried out. The primary objective was to evaluate the possible association between the risk of malnutrition, evaluated at the moment of hospitalisation for respiratory distress caused by a COVID-19 infection, and clinical outcomes such as: mortality, length of stay and morbidity at discharge. The presence of pressure sores, the occurrence of superinfections and the admission to intensive care units were analysed as secondary outcomes.

Inclusion criteria were: adult patients admitted from the Emergency Department with a diagnosis of respiratory distress given by a SARS-CoV-2 infection. Exclusion criteria were: patients who were transferred directly from the Emergency Department to Intensive care units, patients for whom an initial assessment could not be carried out and patients who did not give consent for the use of their personal data for research.

Data of all hospitalised patients admitted directly from the Emergency Department to Humanitas Research Hospital, a university tertiary hospital in Rozzano (Milan, Italy) wards between 1 March and 30 April 2020, when respecting the inclusion/exclusion criteria, were collected retrospectively in May 2020, for a total of 652 patients. The data collected comprehend information about patient general conditions at admission (vital signs, pre-existing comorbidities and concomitant diseases) and nutritional state, with the aim of assigning a value of nutritional risk on the Malnutrition Universal Screening Tool (MUST) complemented with an evaluation of the nutritional state of the patient.

2.1. Literature review and identification of a rating scale for nutritional risk

A literature review was carried out in April 2020, using the main databases. The criteria used for the review were based on the guideline PRISMA statement. The aim of the literature review was to verify if there were any previous studies that had already examined the association between an alteration of the nutritional state and the severity of the disease. The analysed articles [1,18–23] identify malnutrition as a possible risk factor for COVID-19, but, due to the lack of clinical trials and the lack of homogenous large populations to be sampled, this association needs further research [22,23].

From an additional literature review, the MUST index was identified as a primary assessment tool to evaluate the risk of malnutrition in patients that resulted positive for COVID-19 [24]. This tool is quick and easy to apply, with a sensibility of 79% and a specificity of 91% [25]. A systematic review [26] that evaluated the use of different assessment scales for malnutritional risk in COVID-19 positive patients, came to the conclusion that the MUST index and Mini Nutritional Assessment have an increased predictive validity in patients infected with SARS-CoV-2.

The MUST index analyses three criteria: BMI, weight changes in the past 3–6 month and no nutritional intake or likelihood of no intake for more than 5 days associated with an acute illness.

2.2. Statistical analysis

Data were described as number and percentage or mean and standard deviation or median and interquartile range, as appropriated. Adherence to Gaussian distribution was verified with Shapiro–Wilk test. Differences among groups were explored with Kruskal Wallis test or ANOVA, as appropriate. Due to the fact that MUST index was not calculated on obese patients, a subgroup analysis was performed in obese and non-obese patients.

Association with mortality was explored with Cox regression. Independent variables with a p-value under 0.2 were then submitted to a multivariable Cox regression. A p-value under 0.05 was considered significant. All analyses were performed with Stata 15.

Demographic data and outcome measures were collected in an excel sheet in anonymous form and collected by an investigator not involved in assistance, to promote independence in data collection.

The dataset was subdivided in four sections: admission data (gender, age, BMI, vital sign collected in ER, fasting, enteral nutrition activation, weight variation, previous pathologies), MUST value retrospectively calculated by the investigator, hospitalisation data (decubitus lesions, superinfections, oxygen therapy, ICU admission), and discharge data (hospitalisation length, patient status ad discharge).

As for superinfections patients diagnosed with positive blood cultures, pharyngeal swaps and bronchial aspirate were taken into consideration.

The MUST index score was calculated based on the data given on the patient record [25]. Factors that affect the patient for fasting such as: C-PAP, non-invasive ventilation, oxygen masks with an oxygen flow over 10 L/min and Venturi mask with FiO₂ over 50% were taken into consideration.

3. Results

Patients were initially divided into 3 different cohorts: patients that had all hospitalization data documented (n = 529), patients without a measured BMI (n = 96) and patients for whom it was not possible to document the weight variations (n = 27). Between groups comparison has detected statistically significant differences for age (respectively 65.1 ± 14.3 years, vs 73.3 ± 14.2 years; vs 68.3 ± 12.7 years; p < 0.001), enteral nutrition (respectively 18 (3.4%), vs 12 (12.5%), vs 4 (14.8%), p < 0.001) and intubation at admission (respectively 11 (2.1%), vs 11 (11.5%), vs 4 (14.8%), p < 0.001).

The analysis was limited to 515 patients, from whom 353 (68.5%) males, with also discharge complete information. Examining this cohort, we estimated the prevalence of malnutrition using the MUST index, showing an average risk of malnutrition (MUST = 1) in 13 (2.5%) patients and higher risk (MUST ≥ 2) in 80 (15.5%) patients, for a total of patients at risk of 18.1%. The data were analysed dividing the cohort based on the outcome of the disease (Table 1). The multivariable analysis shows that the association between the MUST index with mortality is maintained (HR 1.25, 95% CI 1.04–1.51, p = 0.019) even after the corrections of age, treated hypertension, admission to an intensive care unit and oxygen therapy.

Using the same cohort, we analysed the data for morbidity at discharge: from 515 patients with clinical outcome data at discharge, 358 were discharged, 65 were transferred to other care facilities due to clinical problems and 92 deceased (Table 2). The data show an association with the MUST index score (discharged 0.27 ± 0.68, discharged with problems 0.40 ± 0.93, deceased

Table 1
Association of survival with baseline characteristics of the patients.

	Alive	Deceased	HR (95%CI)	p
N	423	92		
Sex (M)	288 (68.1%)	65 (70.7%)	0.97 (0.62–1.52)	0.899
Age (years)	62.5 ± 13.8	76.9 ± 9.7	1.07 (1.05–1.09)	<0.001
BMI	27.4 ± 5.2	27.0 ± 6.7	0.98 (0.94–1.02)	0.278
Fasting	44 (10.4%)	28 (30.4%)	2.71 (1.73–4.23)	<0.001
Oxygen Therapy	214 (50.6%)	69 (75.0%)	2.13 (1.33–3.43)	0.002
Intubation at T0	3 (0.7%)	7 (7.6%)	3.55 (1.64–7.69)	0.001
Dyspnoea	216 (51.1%)	63 (68.5%)	1.88 (1.21–2.92)	0.005
Arterial hypertension in therapy	179 (42.3%)	69 (75.0%)	2.99 (1.86–4.79)	<0.001
Current neoplasia	22 (5.2%)	19 (20.7%)	3.28 (1.98–5.45)	<0.001
MUST	0.29 ± 0.73	0.64 ± 0.93	1.38 (1.14–1.67)	0.001
ICU	69 (16.3%)	10 (10.9%)	0.31 (0.16–0.61)	0.001

Table 2
Comparison of discharged patients, discharged patients with problems and deceased patients.

	Discharged	Discharged with problems	Deceased	p
N	358	65	92	
Sex (M)	238 (66.5%)	50 (76.9%)	65 (70.7%)	0.222
Age (years)	61.1 ± 13.5	70.0 ± 13.4	76.9 ± 9.7	<0.001
BMI	27.5 ± 5.1	27.1 ± 5.4	27.0 ± 6.7	0.160
Fasting	34 (9.5%)	10 (15.4%)	28 (30.4%)	<0.001
Ongoing enteral nutrition	6 (1.7%)	2 (3.1%)	8 (8.7%)	0.004
Intubation at T0	3 (0.8%)	0	7 (7.6%)	0.001
Dysphagia	4 (1.1%)	7 (10.8%)	4 (4.4%)	<0.001
Arterial hypertension in therapy	141 (39.4%)	38 (58.5%)	69 (75.0%)	<0.001
Current neoplasia	18 (5.0%)	4 (6.2%)	19 (20.7%)	<0.001
MUST	0.27 ± 0.68	0.40 ± 0.93	0.64 ± 0.93	<0.001
Pressure sores	15 (4.2%)	8 (12.3%)	3 (3.3%)	0.032
Superinfections	70 (19.6%)	19 (29.2%)	20 (21.7%)	0.211
Oxygen Therapy	237 (66.2%)	54 (83.1%)	84 (91.3%)	<0.001
NIV-Cpap	48 (13.4%)	18 (27.7%)	26 (28.3%)	<0.001
Hospitalisation days	13 (2–66)	26 (2–59)	14 (7–38)	0.033
Hospitalisation length	11 (3–91)	17 (4–80)	8 (2–69)	<0.001

0.64 ± 0.93, p < 0.001). The MUST index was also associated with complications during hospitalisation. In this case, data indicated that the malnutrition index is not associated with superinfection (OR 1.13, 95% CI 0.88–1.47, p = 0.339), nor with development of pressure sores (OR 1.25, 95% CI 0.81–1.94, p = 0.315). The development of pressure sores and superinfections appears to be directly related to the length of the hospitalisation and the clinical status of the patient (Table 3).

A subgroup analysis was performed on 387 patients, of which 270 (69.8%) males with BMI<30, divided on the outcome alive/deceased. In this analysis the MUST index score was associated with the survival of the patient (HR 1.43, 95% CI (1.17–1.74), p < 0.001). Lastly, we evaluated the data for morbidity at discharge in this subgroup. These patients also showed a statistically significant association of MUST index score and clinical outcome at discharge (data not showed).

Table 3
Secondary outcome (pressure sores and superinfections).

	Pressure Sores		P	Superinfections		p
	Present	Absent		Present	Absent	
N	26	489		109	406	
Sex (M)	19 (73.1%)	334 (68.3%)	0.672	78 (71.6%)	275 (67.7%)	0.445
Age (years)	71.9 ± 13.7	64.7 ± 14.2	0.009	63.0 ± 14.7	65.6 ± 14.1	0.131
BMI	26.6 ± 4.2	27.4 ± 5.6	0.735	27.9 ± 5.9	27.2 ± 5.4	0.329
Fasting	5 (19.2%)	67 (13.7%)	0.390	20 (18.4%)	52 (12.8%)	0.161
Ongoing enteral nutrition	0	16 (3.3%)	1.000	8 (7.3%)	8 (2.0%)	0.009
Oxygen Therapy	20 (76.9%)	263 (53.8%)	0.025	69 (63.3%)	214 (52.7%)	0.048
Intubation at T0	0	10 (2.0%)	1.000	5 (4.6%)	5 (1.2%)	0.040
Dysphagia	2 (7.7%)	13 (2.7%)	0.172	6 (5.5%)	9 (2.2%)	0.101
Arterial hypertension in therapy	17 (65.4%)	231 (47.2%)	0.106	55 (50.5%)	193 (47.5%)	0.588
Current neoplasia	0	41 (8.4%)	0.253	10 (9.2%)	31 (7.6%)	0.556
MUST	0.34 ± 0.77	0.50 ± 0.86	0.243	0.41 ± 0.92	0.33 ± 0.74	0.621
Oxygen Therapy	24 (92.3%)	351 (71.8%)	0.022	89 (81.7%)	286 (70.4%)	0.020
NIV-Cpap	8 (30.8%)	84 (17.2%)	0.109	36 (33.0%)	56 (13.8%)	<0.001
Hospitalisation days	19.5 (16–47)	13 (2–66)	0.022	17 (2–66)	10.5 (2–36)	0.009
Hospitalisation length	36 (6–74)	11 (2–91)	<0.001	19 (2–80)	10 (2–91)	<0.001

In the subgroup of the 128 obese patients, from whom 83 (64.8%) male, the most relevant indicator for outcome from a clinical point of view is the BMI, being directly proportional to mortality.

In patients with a BMI > 30 transferred to other care facilities mortality was associated with age, BMI, intubation, oxygen therapy, dysphagia, as well as an increase in the average length of hospitalisation.

4. Discussion

This study was carried out with the aim of investigating the association between the risk of malnutrition recorded in the Emergency Department and patients hospitalised due to COVID-19, the clinical outcomes of hospitalisation and the morbidity at discharge.

As for the evaluation of the nutritional risk, identified with the MUST index, the data show a close association between the risk score and the gravity of the disease. Therefore, the MUST index could foretell the outcome of the hospitalisation, regardless of the factors named above.

The average score of the MUST index has shown to be higher in patients that were discharged with clinical problems or that deceased, in line with findings in literature, but our sample has a mean age of 65.1 ± 14.3 years, unlike other studies previously published in the literature [1,21,26] which included a sample with higher ages and lower sample numbers, also our sample presented a lower malnutrition risk (an average value in all groups below 1).

Just as in previous studies [27] our study highlighted that arterial hypertension, suffering from a neoplastic disease or hospitalisation in an intensive care unit are risk factors for severe clinical outcomes.

The secondary analysis of obese patients showed an increase in mortality risk directly linked to an increase in age and BMI, underlying diseases like arterial hypertension, diabetes or renal failure were also taken into consideration. These outcomes are confirmed by various articles found in literature that examined this association [28]. This demonstrates that obese patients are at higher risk of a severe evolution of SARS-CoV2 infection and its associated mortality.

A limit of this study is the retrospective nature of the analysis. Another limitation to the study is the fact that the analysis was only carried out on a specific subgroup not representative of the general population, inasmuch the analysed groups patient data available differed. Therefore, the results can only be generalised to a limited extent.

Further studies, possibly prospective researches, are therefore needed to obtain a better comprehension of the impact of malnutrition on the outcome of hospitalised COVID-19 patients.

5. Conclusions

Based on the indications given by literature, this study has shown how malnutritional risk is a negative prognostic factor in terms of mortality, hospitalisation length and clinical status of the patient at discharge in patients that have COVID-19.

Availability of the data and materials

The analysed data is available on demand.

Ethical approval and consent on the participation

Protocol number: CLI 20/02 from 20/05/2020.

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Authors contributions

Stefano Mancin: Conceptualization, Methodology, Writing – Review & Editing, Investigation, Visualization.

Daniela Cattani: Conceptualization, Methodology, Writing – Review & Editing, Investigation, Visualization.

Andrea Bertone: Writing – Original Draft, Investigation, Resources, Visualization.

Emanuela Morengi: Software, Validation, Formal analysis, Data Curation, Visualization.

Beatrice Mazzoleni: Review & Editing, Project administration, Supervision.

Elena Azzolini: Review & Editing, Supervision.

Daniela Donizzetti: Supervision.

Lorena Passadori: Project administration, Supervision.

Fanny Sökeland: Writing – Review & Editing.

All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare the absence of any kind of conflict of interest.

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