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Original article

Combined effect of Controlling Nutritional Status and Acute Kidney Injury on severe COVID-19 short-term outcomes

Effet combiné du l'état nutritionnel et de l'insuffisance rénale aiguë sur le pronostic à court terme des formes sévères de la COVID-19

Salam Bennouar[a,*], Abdelghani Bachir Cherif[b], Amel Kessira[c], Djamel-Eddine Bennouar[c], Samia Abdi[a]

[a] *Central Laboratory of clinical biology, University Hospital center of Blida, 9000 Blida, Algeria*
[b] *Department of Internal Medicine and Cardiology, University Hospital Center of Blida, 9000 Blida, Algeria*
[c] *Department of hemobiology and blood transfusion, University Hospital Center of Annaba, 23000 Annaba. Algeria*

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ABSTRACT

Introduction/Objectives. – Acute kidney injury (AKI) and malnutrition are two complications commonly reported in severe forms of COVID-19, their combined effect on short-term mortality is, however, not yet investigated. The objective of this study is to determine both their individual and combined effects on short-term prognosis.
Materials and methods. – This is a prospective, uni-centric study, including 247 severe COVID-19 patients, admitted between April 25th and June 20th, 2020, at the University Hospital of Blida. AKI was defined according to the KDIGO-2012 guidelines. Nutritional status was assessed using the Controlling Nutritional Status (CONUT) score. The association with in-hospital mortality was assessed using the Kaplan-Meier method and proportional Cox regression.
Results. – Among the 247 severely affected COVID-19 patients included in this study, 34.4% developed AKI, 30.4 and 1.2%, respectively, had moderate and severe CONUT scores, 17.7% worsened and progressed to a critical state and 26.7% did not survive. Both AKI and CONUT score were significantly associated with mortality in a dose-response manner (pLog-Rank < 0.0001). Their relative risks are respectively (HR = 3.25 CI 95% [1.99–5.3] and HR = 2.42 CI 95% [1.5–3.9], $p < 0.0001$). In multivariate analysis, the highest risk was observed for the AKI-CONUT-high combination (HR = 3.0, 95% CI [1.5–6.1], $p = 0.002$).
Conclusion. – A possible synergistic interaction between AKI and CONUT score for COVID-19 short-term mortality has been highlighted. Monitoring of renal function associated with assessment of nutritional status should be performed routinely and systematically from the early stages of admission.

Mots clés :
COVID-19
Acute Kidney Injury
CONUT score
Mortalité à court terme

RÉSUMÉ

Introduction/objectifs. – L'insuffisance rénale aiguë (AKI) et la dénutrition sont deux complications fréquemment retrouvées dans les formes sévères de la Covid-19. L'objectif de cette étude est de déterminer leurs impacts individuels et combinés sur le pronostic à court terme.
Matériel et méthodes. – Il s'agit d'une étude prospective, uni-centrique, incluant 247 cas sévères de Covid-19, admis entre le 25 avril et le 20 juin 2020, au niveau de l'hôpital universitaire de Blida. L'AKI a été définie en suivant les recommandations de la KDIGO-2012. L'état nutritionnel a été évalué en utilisant le score « Controlling Nutritional Status » (CONUT). L'association avec la mortalité en milieu hospitalier a été évaluée par la méthode de Kaplan-Meier et la régression proportionnelle de Cox.

* Corresponding author. Central laboratory of clinical biology. Frantz Fanon Hospital, University Hospital Center of Blida, 9000 Blida, Algeria.
E-mail addresses: salambennouar@gmail.com (S. Bennouar), salam_phr2004@yahoo.fr (A. Bachir Cherif), Kessira.am@gmail.com (A. Kessira), djameledinebennoua@gmail.com (D.-E. Bennouar), Samia.abd@gmail.com (S. Abdi).

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Résultats. – L'incidence de l'AKI était de 34,4 %, 50% avaient une dénutrition modérée à sévère. L'AKI et le score CONUT étaient significativement associés à la mortalité d'une manière dose à effet ($p_{Log\text{-}Rank}$ < 0,0001). Leurs risques relatifs étaient respectivement (HR = 3,25 CI 95 % [1,99–5,3] et HR = 2,42 CI 95 % [1,5–3,9], p < 0,0001). En analyse multivariée, le risque le plus élevé est observé pour la combinaison AKI-CONUT-high (HR = 3,0, CI 95% [1,5–6,1], p = 0,002).
Conclusion. – Une interaction de type synergétique a été mise en évidence entre l'AKI et le score CONUT pour la mortalité à court terme due à la Covid-19. La surveillance de la fonction rénale associée à l'évaluation de l'état nutritionnel devrait être effectuée systématiquement dès les premiers stades d'admission.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease with an unprecedented worldwide spread rate. Of widely varied symptomatology, most infected patients either remain asymptomatic or evolve into a mild to moderate form, which usually has a favorable clinical course. In certain cases, severe to critical forms may occurs requiring recourse to Intensive Care Unit (ICU) services and may be potentially life-threatening. Most recent published reports have indicated that the mortality rate of these severe forms can be as high as 30–70% [1–3].

In dealing with this pandemic, the most challenging task facing clinicians is to avoid progression to severe forms [4]. It is therefore urgent to identify the clinical and biological conditions associated with a poor prognosis. This will enable a better risk stratification at an early stage and an optimization of medical care in an effort to ultimately improve the survival prognosis.

Acute kidney injury (AKI) and malnutrition are two common conditions encountered in severe and critical forms of COVID-19 [1,5–7]. The Controlling Nutritional Status score (CONUT) is a new nutritional assessment tool that is easily calculated from laboratory data [8,9], its validation has been carried out in previous studies [8–10]. Although the prognostic value of these two complications is well recognized in the ICU [6,11,12], their combined effect on the short-term outcome of severe and critical cases of COVID-19 has never been investigated.

The aim of this study is to assess the incidence of AKI and malnutrition, as defined by a CONUT-high score, in severely affected COVID-19 patients and to explore their individual and combined effects on short-term prognosis.

2. Materials and methods

2.1. Patients and Study Setting

In Algeria, the Blida province is considered as the outbreak epicenter, hosting the highest number of confirmed cases and deaths by COVID-19 [13]. This is a prospective, single-center, cohort study, including severely COVID-19-affected subjects who were admitted between 25th April and 20th June 2020 to the Reanimation-Anesthesia Department of the Frantz Fanon Hospital of the Blida University Hospital Center. This department, which holds an ICU, has been fitted out by the local authorities to take charge of severe and critical COVID-19 forms. Bio-monitoring was carried out in the laboratory of medical-surgical emergencies. Ineligibility criteria were: age < 18 years, patients died or transferred within 48 hours of admission, pregnancy, patients requiring dialysis before admission, and ongoing tumor processes. This study was conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived given the context of the fast emergence of this infectious disease.

2.2. Confirmatory diagnosis, severity definition and endpoint

The diagnosis of COVID-19 was carried out at Algiers Pasteur Institute through the Real-Time Reverse Transcription Polymerase Chain Reaction technique (RT-PCR). Following the World Health Organization protocol (WHO) [14], samples from nasal and pharyngeal swabs were tested for this purpose. Severe form has been defined by the presence of one of the following criteria: 1) shortness of breath: respiratory rate > 30 breaths/min in the resting state; 2) pulse oxygen saturation <93% or 3) arterial blood oxygen pressure (PaO2)/oxygen concentration (FIO2) < 300 mmHg. Critical form in the presence of one of the following criteria: 1) respiratory failure requiring mechanical ventilation; 2) shock or 3) multi-organ failure requiring ICU [6,15,16]. The final endpoint was in-hospital mortality within 28 days following admission. Clinical diagnoses as well as nasal and pharyngeal swabs were performed by the treating physicians.

2.3. Biomarkers and Biological Definitions

All patients were tested on admission and then periodically every 48 hours for the following biological parameters: inflammatory markers: C-reactive protein (CRP), ferritin and total blood count. Blood glucose, markers of renal function: blood urea nitrogen (BUN), serum creatinine (Scr) and electrolytes (Sodium and Potassium). Nutritional biomarkers: albumin, total proteins and total cholesterol. Enzymes and hepatic markers: total bilirubin, lactate dehydrogenase (LDH), glutamo-oxaloacetic transaminase (GOT), glutamo-pyruvic transaminase (GPT), gamma-glutamyl-transpeptidase (γ-GT) and alkaline phosphatases (ALP). Biological monitoring was carried out in the same laboratory: the laboratory of medical-surgical emergencies of the Frantz Fanon Hospital.

Baseline Scr was defined as the first value recorded at admission [17]. Elevated baseline Scr was defined according to the laboratory reference values by a serum level greater than: 115 μmol/l (13 mg/l) and 94 μmol/l (11 mg/l) for men and woman respectively, elevated BUN by a serum level greater than 8.3 mmol/l (0.5 g/l) for both genders.

AKI, occurring during the hospitalization, was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria by: an increase in Scr by 26.5 μmol/l (3.0 mg/l) over 48 hours or a 50% increase over 7 days. Following the KDIGO 2012 guidelines, AKI was classified in three stages: stage 1: increase of Scr ≥ 3.0 mg/l (26.52 μmol/l) or ≥ 1.5- to twofold from baseline, or urine output <0.5 ml/kg/h for more than 6 hours, stage 2: increase of Scr > two- to threefold from baseline, or urine output <0.5 ml/kg/h for more than 12 hours, and stage 3: Increase of Scr > threefold from baseline or ≥ 40 mg/l (353.60 μmol/l) or urine output <0.3 ml/kg/h for more than 24 hours or Anuria for more than 12 hours [17].

The CONUT score was calculated based on the serum albumin concentration, total blood cholesterol level and total peripheral

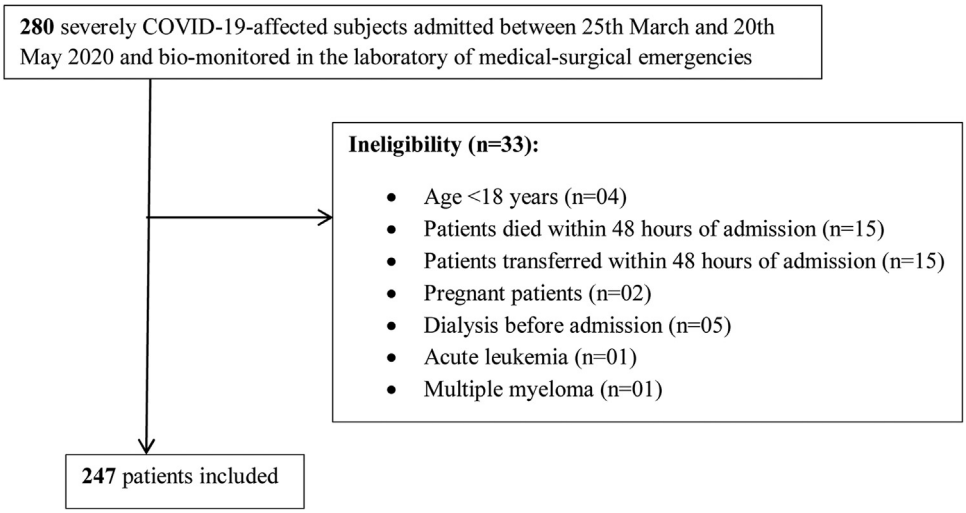

Fig. 1. Flow chart of patients in the study.

lymphocyte count as measured within 24 hours of admission. Nutritional status was determined using the scoring criteria (12 points maximum) as follows: CONUT-normal: [0–1] points, CONUT-mild: [2–4] points, CONUT-moderate: [5–8] points and CONUT-severe: [9–12] points [8,9]. Hypoalbuminemia and hypocholesterolemia were defined as a serum level less than 35 g/l and 3.62 mmol/l (1.4 g/l) respectively [8–10].

2.4. Statistical analysis

Statistical analysis was performed with SPSS version 25.0 software (IBM SPSS). The Shapiro-Wilk test was used to analyze the distribution of continuous variables. Continuous variables are presented as Means ± Standard Deviations or Medians (interquartile range) and are compared by the Student t-test or Mann-Whitney U-test according to the normality of the distribution. Qualitative variables are described as number (percentages) and are compared by the Pearson $\chi 2$ test.

Survival and cumulative hospital mortality rates were compared across the predefined groups using the Kaplan-Meier approach. The plots were further compared using the Log Rank test. The association of independent variables with in-hospital mortality was assessed by uni-variate and multi-variate proportional Cox regression analysis. The variables included in the adjustment model are those associated with in-hospital mortality in the uni-variate model ($p < 0.1$).

For all statistical tests, a p value of less than 0.05 is assumed to be statically significant.

3. Results

3.1. Characteristics of the study population

After applying the exclusion criteria (Fig. 1), a total of 247 patients were enrolled in this study. The study population characteristics are presented in Table 1. The majority of patients were males (67.6%), mean age was 64.9 ± 10.6 years. Within the 247 severely affected COVID-19 patients, 34.4% developed AKI, distributed as follows: stage 1: 32.9%, stage 2: 34.1%, and stage 3: 32.9%. Among the study population, 30.4 and 1.2% of patients, respectively, had moderate and severe CONUT scores, 17.7% worsened and progressed to a critical state requiring admission to ICU with either invasive or non-invasive mechanical ventilation and 26.7% did not survive. The mean duration from ICU admission until death was 8.6 ±7.1 days, with a range of [03–28] days.

As shown in Table 1, the deceased patients were significantly older (69.1 ± 10.3 *vs.* 63.4 ± 10.3 years, $p < 0.0001$), the majority of those deceased had developed AKI (59.1 *vs.* 25.4%, $p < 0.001$), half of them were in the moderate and severe CONUT groups (47% vs. 24.3% and 3% *vs.* 0.6%, $p < 0.0001$), respectively, and over a third had progressed to a critical state (37.9 *vs.* 9.9%, $p < 0.0001$). As expected, there was a significant difference in initial biologic status between the deceased and non-deceased patients: deceased patients were admitted with remarkably higher levels of inflammatory markers (CRP, ferritin, white blood cells and neutrophils), blood glucose and renal function markers (Scr, BUN), enzymes and liver markers (LDH, GOT, GPT, GGT, PAL and bilirubin). In addition, these patients had significantly lower levels of natremia, platelets, and nutritional markers (total cholesterol, albumin, total protein and red blood cells).

3.2. AKI, CONUT and in-hospital mortality rates:

Fig. 2 (a, b) shows the mortality rate based on the CONUT score and the onset of AKI. The CONUT score was significantly related to mortality in a dose-response manner (p for trend < 0.0001). The lowest mortality rate was observed in the CONUT-normal group (13.3%), then it increased gradually across groups; the highest mortality rate was observed in the CONUT-severe group (66.7%).

Likewise, AKI occurring over the course of hospitalization appears to be strongly linked to a considerable reduction in survival rate (Fig. 2a: 54.1% vs. 83.3%, $p < 0.0001$), as shown in Table 1, the mortality rate increases linearly with the stage of AKI; the highest mortality rate was reported in patients who progressed to stage 3 of AKI (46.2%, $p = 0.016$). The Kaplan-Meier survival curve analysis for cumulative crude in-hospital mortality confirms the prognostic quality of these two factors. Indeed, curves seemed to significantly diverge within the first days of hospitalization ($p_{Log\text{-}Rank} < 0.0001$), thereby indicating a reduced probability of survival in the at-risk groups (Fig. 3a, b).

3.3. AKI, CONUT and short-term mortality risk

The relative risk for short-term mortality related to AKI and CONUT was assessed through uni-variate and multi-variate proportional Cox regression. Given the limited number of patients in the CONUT-severe group, Cox regression was conducted after pooling

Table 1
Biological characteristics and outcomes of severely affected COVID-19 patients.

	Total $n = 247$	Non-Survivors $n = 66$ (26.7)	Survivors $n = 181$ (73.3)	*P*
Male gender n (%)[†]	167 (67.6)	51 (77.3)	116 (64.1)	0.05
Age (years)	64.9 ± 10.6	69.1 ± 10.3	63.4 ± 10.3	**< 0.0001**
RBC (10^6 e/μl)	4.38 ± 0.81	4.15 ± 0.88	4.47 ± 0.77	**0.013**
Hemoglobin (g/dl)	12.5 ± 2.1	12.1 ± 2.4	12.7 ± 2.02	0.11
WBC (10^3 e/μl)	11.4 ± 7.1	14 ± 6.53	10.5 ± 7.1	**< 0.0001**
Lym count (10^3 e/μl)	1.3 ± 0.93	1.24 ± 0.67	1.3 ± 1.01	0.41
Neut count (10^3e/μl)	9.3 ± 6.4	11.9 ± 6.2	8.4 ± 6.2	**< 0.0001**
Platelet (10^3 e/μl)	300 ± 136	251 ± 113	318 ± 139	**< 0.0001**
CRP (mg/l)	38.9 ± 33.3	85.5 ± 27.6	21.9 ± 12.6	**< 0.0001**
Ferritin (ng/ml)	494.3 ± 231	663.8 ± 222	432.5 ± 202	**< 0.0001**
Glucose (mmol/l)	10.3 ± 5.6	12.3 ± 7.2	9.7 ± 4.8	**0.001**
BUN (mmol/l)	12 ± 9.1	16.4 ± 10.5	10.3 ± 8.0	**< 0.0001**
SCr (μmol/l)	167 ± 144	204 ± 173	154 ± 130	**0.013**
Sodium (mmol/l)	134.1 ± 6.1	129.2 ± 7.1	135.9 ± 4.6	**< 0.0001**
Potassium (mmol/l)	4.21 ± 0.83	4.3 ± 0.95	4.18 ± 0.78	0.25
LDH (IU/l)	495 ± 358.5	655.5 ± 426	436.8 ± 311	**< 0.0001**
GOT (IU/l)	76 ± 122	127.7 ± 216	57.8 ± 47.7	**< 0.0001**
GPT (IU/l)	53 ± 96.9	86.9 ± 173	41.4 ± 37.4	**0.001**
γ-GT (IU/l)	55.5 ± 69.8	76 ± 118.1	48.1 ± 37.8	**0.006**
ALP (IU/l)	186 ± 186	228.7 ± 323	170.8 ± 91	**0.038**
TB (μmol/l)	15.8 ± 21.9	47 ± 71	21 ± 11	**< 0.0001**
Albumin (g/l)	34.7 ± 5.7	30 ± 4.5	36.5 ± 5.1	**< 0.0001**
Total Protein (g/l)	67.5 ± 8	62 ± 7.7	69.5 ± 7.2	**< 0.0001**
TC (mmol/l)	3.67 ± 0.93	3.25 ± 0.77	3.83 ± 0.95	**< 0.0001**
SpO_2 (%)	90.1 ± 1.1	87.0 ± 3.0	91.2 ± 1.3	**< 0.0001**
Critical cases n (%)[†]	43 (17.7)	25 (37.9)	18 (9.9)	**< 0.0001**
AKI n (%)[†]	85 (34.4)	39 (59.1)	46 (25.4)	**< 0.0001**
AKI stages n (%)[†]				
1	28 (32.9)	9 (23.1)	19 (41.3)	**0.016**
2	29 (34.1)	12 (30.8)	17 (37.0)	
3	28 (32.9)	18 (46.2)	10 (35.7)	
CONUT n (%)[†]				
1	30 (12.1)	04 (6.1)	26 (14.4)	
2	139 (56.3)	29 (43.9)	110 (60.8)	**< 0.0001**
3	75 (30.4)	31 (47)	44 (24.3)	
4	3 (1.2)	02 (03)	01 (0.6)	
Survival duration (Days) [min-max]	8.6 ±7.1 [03–28]	–	**–**	

AKI: acute kidney injury, ALP: alkaline phosphatases, BUN: blood urea nitrogen, CONUT: Controlling Nutritional Status, CRP: C-reactive protein, GOT: glutamo-oxaloacetic transaminase, GPT: glutamo-pyruvic transaminase, γ-GT: gamma-Glutamyl-Trans-peptidase, LDH: lactate dehydrogenase, Lym count: lymphocyte count, Neut count: neutrophils count, RBC: red blood cells, SCr: serum creatinine, SpO_2: pulse oxygen saturation, TB: total bilirubin, TC: total cholesterol, WBC: white blood cells. p: Student test. Bold values represent significant associations (p<0.05)

[†] p: Pearson's $\chi 2$ test.

Table 2
Univariate and multivariate Cox regression analysis of association between AKI, CONUT score, Their components and in-hospital death in severely affected COVID-19 patients.

	Model 1		Model 2		Model 3	
	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*
Kidney biomarkers						
Non-AKI	1	–	1	–	1	–
AKI	3.25 [1.99–5.3]	**< 0.0001**	3.2 [1.94–5.28]	**< 0.0001**	2.03 [1.17–3.6]	**0.012**
Normal baseline Scr	1	**–**	1	**–**	1	**–**
Elevated baseline Scr	2.85 [1.7–4.76]	**< 0.0001**	3.01 [1.78–5.1]	**< 0.001**	1.9 [1.1–3.4]	**0.027**
Normal baseline BUN	1	**–**	1	**–**	1	**–**
Elevated baseline BUN	3.3 [1.9–5.7]	**< 0.0001**	3.26 [1.87–5.6]	**< 0.0001**	2.4 [1.35–4.3]	**0.003**
Serum nutritional related biomarkers						
CONUT-low	1	**–**	1	**–**	1	**–**
CONUT-high	2.42 [1.5–3.9]	**< 0.0001**	2.36 [1.45–3.8]	**0.0001**	1.87 [1.12–3.2]	**0.018**
Normal baseline albumin	1	**–**	1	**–**	1	**–**
Decreased baseline albumin	9.8 [4.45–21.4]	**< 0.0001**	9.43 [4.3–20.7]	**< 0.0001**	8.9 [3.9–20.1]	**< 0.0001**
Normal baseline TC	1	**–**	1	**–**	1	–
Decreased baseline TC	1.74 [1.07–2.8]	**0.024**	1.78 [1.1–2.9]	**0.02**	1.5 [0.9–2.5]	0.12
Normal baseline Lym Count	1	–	1	**–**	1	–
Decreased baseline Lym count	0.98 [0.61–1.6]	0.95	0.95 [0.6–1.54]	0.83	0.87 [0.53–1.42]	0.57

AKI: acute kidney injury, BUN: blood urea nitrogen, CONUT: Controlling Nutritional Status, Lym count: Lymphocytes count, Scr: serum creatinine, TC: total cholesterol. Model 1: unadjusted model, Model 2: adjusted for age and sex, Model 3: adjusted for the disease severity, blood glucose, GOT, CRP and LDH. HR: Hazard ratio, 95% CI: 95% confidence interval. Bold values represent significant associations (p<0.05)

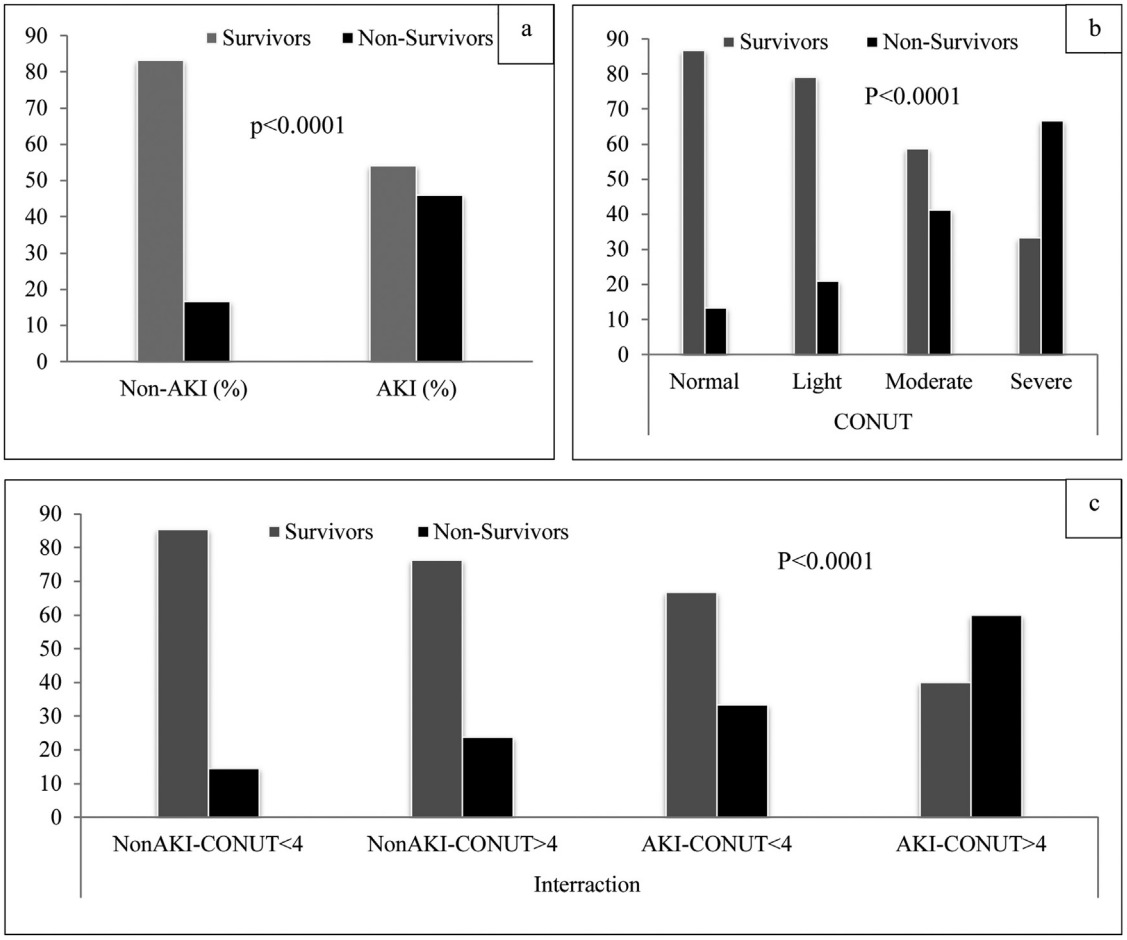

Fig. 2. In-hospital mortality rate of severely affected COVID-19 patients by: a) AKI, b) CONUT score, c) and their interaction.

patients into two groups: CONUT-low (CONUT-normal + CONUT-mild) and CONUT-high (CONUT-moderate + CONUT-severe). Similar models were used to further assess relative risks attributed to their respective components. The results are shown in Table 2.

In the unadjusted model, the acquired AKI during hospitalization and the admission with a CONUT-high score were found to have a crude hazard ratio (HR) for in-hospital mortality about 3.25 and 2.42 times higher respectively, (AKI: HR = 3.25, 95% CI [1.99–5.3], $p < 0.0001$. CONUT-high: HR = 2.42, 95% CI [1.5–3.9], $p < 0.0001$), adjustment for age and sex didn't affect this risk. However, after further adjustment for the disease severity, blood glucose, GOT, CRP and LDH, relative risks dropped to 2.03 and 1.87 respectively, although statistical significance was still maintained (AKI: Adjusted HR = 2.03, 95% CI [1.17–3.6], $p = 0.012$). CONUT-high: Adjusted HR = 1.87, 95% CI [1.12–3.2], $p = 0.018$).

Similarly, the uni- and multi-variate Cox regression shows that high baseline creatinine and urea levels, as well as low albumin and total cholesterol levels, were significantly associated with a higher risk of short-term mortality. Hypoalbuminemia was the most important determinant of short-term mortality with the highest relative risk. However, no significant association was found between baseline lymphocyte count and mortality risk (Table 2).

3.4. Combined effect of AKI and CONUT-high on short-term mortality risk

In the light of the survival and Cox regression analysis described above, both AKI and CONUT-high have been identified as poor short-term prognostic factors. So, what about their combined effect? In order to clarify the relationship between AKI, CONUT-high and short-term mortality, the population was divided into four groups: G1: Non-AKI CONUT-low, G2: Non-AKI CONUT-high, G3: AKI CONUT-low and G4: AKI CONUT-high. Fig. 2c illustrates the mortality rate across these four groups, among patients of non-AKI group; the mortality rate was higher in the CONUT-high subgroup (23.7% vs. 14.5%). Similarly, in the AKI group, the mortality rate was higher in the CONUT-high subgroup (60% vs. 33%).

Analysis of the Kaplan-Meier survival curve (Fig. 3c) demonstrates that the mortality rate differed significantly across these four groups, with Group 4 showing a notable divergence observed within the first few days of admission and explained by a reduced survival probability (p Log-Rank < 0.0001).

Table 3 shows the relative risks of these 4 groups in regard of short-term mortality. Group 1, which has the lowest incidence of mortality, was taken as a reference. In uni-variate analysis, the AKI CONUT-low and AKI CONUT-high groups were significantly associated with a 2.5 and 5.4 risk, respectively, of higher short-term mortality.

This association remains irrespective of the patients' age and gender. However, after final adjustment for confounding factors, only the AKI CONUT-high combination was significantly associated with a risk of short-term mortality, estimated by HR =3.0, 95% CI [1.5–6.1], $p = 0.002$. This suggests a possible interactive effect between AKI and nutritional status on the short-term prognosis of severely affected COVID-19 patients.

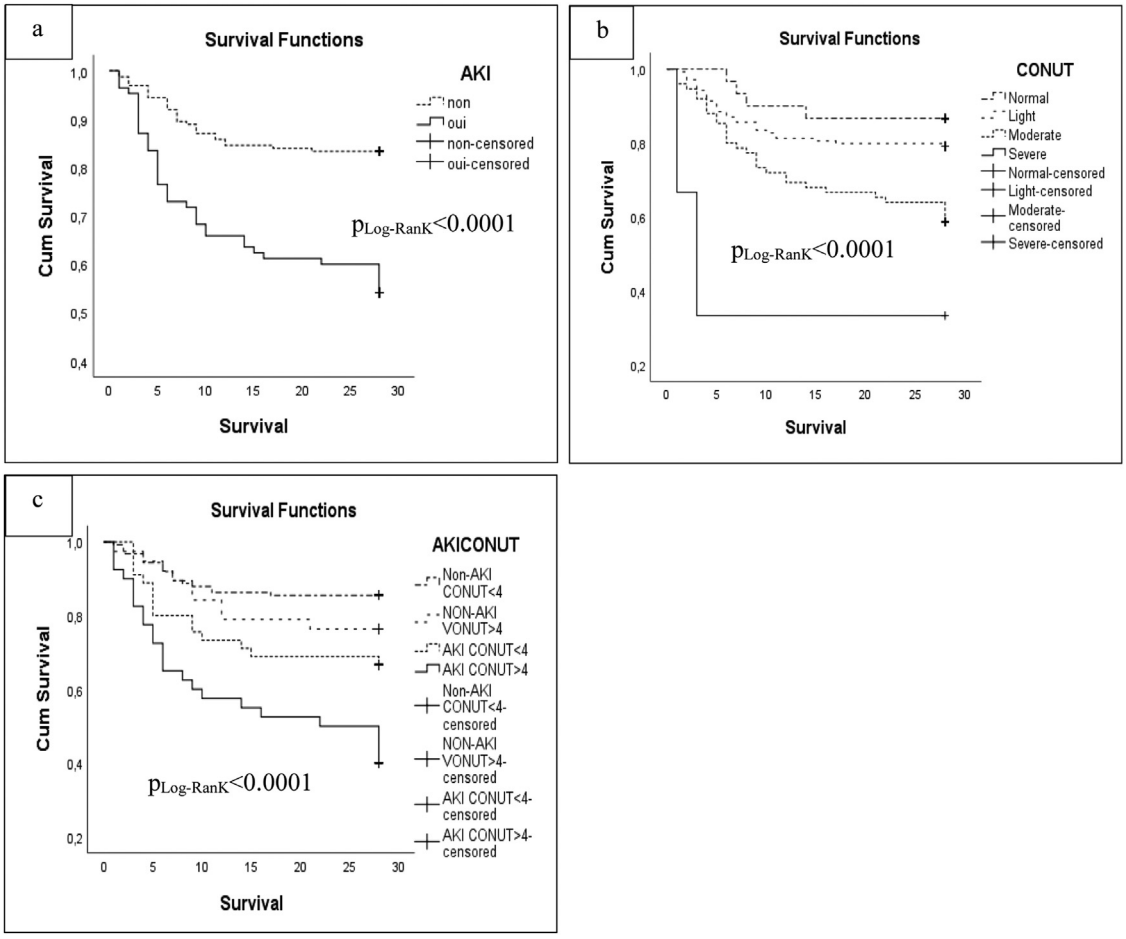

Fig. 3. Kaplan-Meier curve for crude cumulative in-hospital mortality by: a) AKI, b) CONUT score, c) and their interaction.

Table 3
Univariate and multivariate Cox regression analysis of association between AKI-CONUT score combination and in-hospital death in severely affected COVID-19 patients.

	Model 1		Model 2		Model 3	
	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*
Non-AKI CONUT-low	1	–	1	–	1	–
Non-AKI CONUT-high	1,67 [0.75–3.71]	0.21	1.7 [0.76–3.8]	0.19	1.63 [0.73–3.6]	0.23
AKI CONUT-low	2.54 [1.3–5.04]	**0.008**	2.6 [1.3–5.13]	**0.007**	1.8 [0.83–3.8]	0.13
AKI CONUT-high	5.4 [2.9–9.9]	**<0.0001**	5.32 [2.8–9.9]	**< 0.0001**	3.02 [1.5–6.1]	**0.002**

Model 1: unadjusted model, Model 2: adjusted for age and sex, Model 3: adjusted for the disease severity, blood glucose, GOT, CRP and LDH. AKI: acute kidney injury, CONUT: Controlling Nutritional Status. HR: Hazard ratio, 95% CI: 95% confidence interval. Bold values represent significant associations (p<0.05)

4. Discussion

This is a prospective, uni-centric, cohort study including 247 severely affected COVID-19 patients. The most relevant results from this study are presented by the presence of a positive link between the unfavorable nutritional profiles as estimated at admission- defined by a CONUT-high score, the onset of AKI during hospitalization and short-term COVID-19 related mortality. In addition, a possible synergistic interaction was also postulated between AKI and CONUT-high score. To our knowledge, this study is the first to explore the combined effect of AKI and malnutrition on the short-term prognosis of severely affected COVID-19 patients.

This study reports a relatively high, but quite expected, rate of mortality by COVID-19, indeed, current epidemiological investigations suggest that COVID-19 mortality rate appears to be 20 times higher among severely affected patients [2,4], moreover, according to the majority of recently published reports, a mortality rate between 30 and 70% would be expected for COVID-19 patients treated in intensive care units [1,3]. In addition, this mortality rate could be, in part, explained by the advanced age of our population with the many co-morbidities and complications that may be associated.

The AKI is a commonly reported complication in association with COVID-19, particularly in severe and critical cases [1,18]. According to a recently published study [5], AKI was found in 3 to 29% of COVID-19 cases, a rate that is much lower than that observed in our population. The wide discrepancy between the reported incidences is most likely attributable to the non-uniformity of AKI definitions and the high heterogeneity of studied patients, especially with regard to age, co-morbidities and symptomatology severity.

Also, it has been reported that high levels of renal markers (BUN and Scr), assessed as early as the admission phase, as well as sudden loss of kidney function, are powerful predictors of poor short-term COVID-19 outcomes [6,18,19]. This sudden loss of renal function is likely to be multifactorial [5,6], triggered by

a direct cellular infiltration by the SARS-COV-2 virus, in fact, it has been shown that this virus uses the angiotensin converting enzyme 2 (ACE2) receptor pathway as an intracellular gateway [1,20,21], these receptors are particularly abundant in the urinary tract, where they are over 100 times more available than in the respiratory organs [6]. Other indirect mechanisms may also be involved, such as those secondary to hemolysis, rhabdomyolysis, cardio-renal syndrome, hypoxia, hypo-perfusion, and various inflammatory processes exacerbated in response to the viral infection or bacterial superinfection [5,18,22].

In our population of study, one-third of the enrolled patients and half of those who did not survive were classified in the CONUT-high group, indicating a nutritional imbalance in favor towards malnutrition. The very few studies exploring nutritional status among COVID-19 patients reported a prevalence broadly similar to ours. Li et al have assessed the nutritional status of 182 COVID-19 patients aged over 65 years, the authors found a malnutrition rate of 52.7% [23]. Likewise, in the study by Brugliera et al., 45% of patients were reported to be at high nutritional risk [24].

In hospital settings, most nutritional imbalances are the result of increased energy demands (inflammation, stress-related catabolism), whether or not combined with decreased nutrient intake [7,25]. In the case of COVID-19, several mechanisms may be implicated. In particular, COVID-19 is often marked by digestive symptoms such as nausea, loss of taste and smell, vomiting and diarrhea affecting food swallowing, digestion and even absorption [22,23,26]. These gastrointestinal signs may be a direct consequence of viral invasion, as it has been shown that ACE2 is widely expressed in the gastrointestinal tract, making the latter a potential viral target [23]. On the other hand, the exacerbation of inflammatory reactions, fever, stress and anxiety are all conditions that lead to a loss of appetite, and thus contribute to the occurrence of a malnutrition state [23,26].

A positive association has been found between malnutrition state, defined by a CONUT-high score, and short-term mortality, this is in line with all published studies regardless of which tool has been used to assess nutritional status and independently of the underlying medical reasons for hospitalization [15,23,27,28]. Regarding the three components of the CONUT score, albumin seems to be the strongest predictor. It is worth noting, however, that serum albumin is not solely considered as a nutritional marker, but more as an indicator of severity and poor prognosis. In spite of its relatively lengthy half-life time, and its low turnover, its measurement is recommended as early as the first admission stage [7,25,29] given its rapid decrease in blood, especially in inflammatory states, where it is mainly induced by a redistribution towards the interstitial space due to increased capillary permeability [29,30]. In addition, the production of acute phase proteins (such as CRP, ferritin and interleukin. . .) requires the consumption of pre-existing proteins like albumin and even muscle proteins in extreme situations [7,23].

Besides hypoalbuminemia, hypocholesterolemia was also found to be closely related to short-term mortality risk. Although the prognostic value of hypocholesterolemia and decreased lipoprotein levels is well known in the hospital setting, particularly in ICU [31,32], its association with the severity of COVID-19 is only anecdotally evoked. Wei et al. [33] have found a significant decrease in lipid levels (total cholesterol and lipoproteins) upon the onset of first symptoms; moreover this decrease was correlated to the severity. In clinical practice, hypocholesterolemia is quite uncommon; its pathophysiological mechanism is not yet completely elucidated [31]. However, its association with inflammatory states, particularly those induced by viral infections, has been repeatedly mentioned in the course of HIV, hepatitis B, dengue virus and SARS infections [33]. In these cases, the drop in cholesterol levels is most probably secondary to pro-inflammatory cytokines, which disrupt lipid metabolism while impairing hepatic function, lowering the blood flow of lipoproteins and enhancing their capture by tissues, in addition, the vulnerability of lipid particles to free radicals' pro-oxidant effects may also be a contributory factor [33].

The combined effect of AKI and malnutrition on poor prognosis is not often described in the available research [11], and even less so for COVID-19 patients. One of the most relevant findings of this study is the highlighting of a synergistic interaction between these two conditions for short-term prognosis. An appropriate medical nutritional approach to AKI patients is essential for improving their vital prognosis, especially since adequate parenteral or enteral nutrition has previously been shown to improve renal function, as well as adequate protein intake to reduce tubular damage and boost the immune system [11,22,28].

The results of this study should be interpreted with recognition of a certain limitations. First, this is a single-centric study, hence studies with a larger sample sizes are encouraged. Second, the assessment of nutritional status was carried out exclusively by blood tests, it was difficult to collect additional data on dietary behavior, body composition, recent weight loss and physical activity given the proportion of patients mechanically ventilated or under sedation, such data could have been helpful in computing other recommended Scores. Third, the diagnosis of kidney injury as well as proteinuria values was not documented in this study. Indeed, COVID-19 can induce nephrotic syndromes and collapsing glomerulopathy, manifested by a high flow proteinuria. In this case, hypoalbuminemia, the main determinant of high CONUT score, could therefore be a consequence of glomerular injuries caused by SARS-CoV-2 infection rather than an indicator of the patients' nutritional status. Further investigations involving urinary sediment and anatomopathological analyses are therefore needed to clarify the interaction between nutritional status and renal damage on the prognosis of COVID-19 patients.

5. Conclusion

Malnutrition is very common in patients with severe COVID-19 and is closely linked to an increased risk of in-hospital mortality, particularly in patients who subsequently acquire AKI. Taken together, findings outlined from this study suggest that the initial biochemical assessment provides a useful tool of risk stratification for COVID-19 patients. Nutritional status assessment should be carried out systematically from the early stages of admission. In addition, more frequent serum creatinine testing should be conducted in all patients to increase the likelihood of early AKI diagnosis. Nutritional interventions should be initiated in order to improve the vital prognosis.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Disclosure of interest

The authors have no conflicts of interest to declare.

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