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Original article

Evaluation of Nutritional Practices in the Critical Care patient (The ENPIC study): Does nutrition really affect ICU mortality?

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SUMMARY

Background & aims: The importance of artificial nutritional therapy is underrecognized, typically being considered an adjunctive rather than a primary therapy. We aimed to evaluate the influence of nutritional therapy on mortality in critically ill patients.
Methods: This multicenter prospective observational study included adult patients needing artificial nutritional therapy for >48 h if they stayed in one of 38 participating intensive care units for ≥72 h between April and July 2018. Demographic data, comorbidities, diagnoses, nutritional status and therapy

Abbreviations: EN, Enteral nutrition; ENPIC, Evaluation of Nutritional Practices in the Critical Care; ICU, Intensive care unit; LOS, Length of stay; NUTRIC, Nutrition Risk in the Critically Ill; PN, Parenteral nutrition; RRT, Renal replacement therapies; SAPS, Simplified Acute Physiology Score; SGA, Subjective Global Assessment; SOFA, Sequential Organ Failure Assessment.

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(type and details for ≤14 days), and outcomes were registered in a database. Confounders such as disease severity, patient type (e.g., medical, surgical or trauma), and type and duration of nutritional therapy were also included in a multivariate analysis, and hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported.

Results: We included 639 patients among whom 448 (70.1%) and 191 (29.9%) received enteral and parenteral nutrition, respectively. Mortality was 25.6%, with non-survivors having the following characteristics: older age; more comorbidities; higher Sequential Organ Failure Assessment (SOFA) scores (6.6 ± 3.3 *vs* 8.4 ± 3.7; *P < 0.001*); greater nutritional risk (Nutrition Risk in the Critically Ill [NUTRIC] score: 3.8 ± 2.1 *vs* 5.2 ± 1.7; *P < 0.001*); more vasopressor requirements (70.4% *vs* 83.5%; *P=0.001*); and more renal replacement therapy (12.2% *vs* 23.2%; *P=0.001*). Multivariate analysis showed that older age (HR: 1.023; 95% CI: 1.008−1.038; *P=0.003*), higher SOFA score (HR: 1.096; 95% CI: 1.036−1.160; *P=0.001*), higher NUTRIC score (HR: 1.136; 95% CI: 1.025−1.259; *P=0.015*), requiring parenteral nutrition after starting enteral nutrition (HR: 2.368; 95% CI: 1.168−4.798; *P=0.017*), and a higher mean Kcal/Kg/day intake (HR: 1.057; 95% CI: 1.015−1.101; *P=0.008*) were associated with mortality. By contrast, a higher mean protein intake protected against mortality (HR: 0.507; 95% CI: 0.263−0.977; *P=0.042*).

Conclusions: Old age, higher organ failure scores, and greater nutritional risk appear to be associated with higher mortality. Patients who need parenteral nutrition after starting enteral nutrition may represent a high-risk subgroup for mortality due to illness severity and problems receiving appropriate nutritional therapy. Mean calorie and protein delivery also appeared to influence outcomes.

Trial registration: ClinicaTrials.gov NCT: 03634943.

1. Introduction

The inflammatory response to surgery, trauma, or any severe medical condition causes metabolic disturbances (e.g., protein catabolism) in patients admitted to intensive care units (ICUs) [1]. In conjunction, difficulty achieving adequate nutritional targets in clinical practice may expose patients to nutritional risk or a worsening of preexisting malnutrition [2−4], both of which are associated with a higher incidence of complications and mortality [5−7]. Nutritional therapy not only provides the substrates to preserve organ function but also helps modulate the inflammatory response, optimizes the metabolic status, and ultimately provides substantial benefit in terms of survival and outcome [5,6]. However, some trials have reported harmful effects, and the beneficial effect of nutrition on mortality is underrecognized due to these controversial results [8].

It is not always possible to provide evidence of the benefit of nutrition in ICUs. Several factors related to nutritional therapy, such as the macronutrient dose (i.e., calories and proteins), delivery route (i.e., enteral [EN] and parenteral nutrition [PN]), and initiation time, with each having the potential to affect treatment effectiveness and explain the lack of positive results in some trials [5,6]. EN is the preferred delivery route for patients in ICU, but there is huge variation in how nutritional therapy is provided clinically. Moreover, difficulty persists in meeting the nutritional targets established in clinical practice guidelines, even in randomized control trials (RCTs) [9−15]. Thanks to technical advances and lower rates of associated infection, PN is now considered as safe as EN and may provide optimal delivery of nutrients [9]. Another issue that affects the perceived benefit of nutritional therapy is its duration during the ICU stay. The impact of nutrition may seem less important in those with shorter stays, lower nutritional risks, and less severe critical illness [5,6,16]. Thus, we must consider all these factors in clinical ICU settings when evaluating the impact of nutrition on mortality, especially those associated with the delivery route and duration of therapy.

The primary aim of this study was to estimate the effect on mortality of the different features of artificial nutrition therapy during ICU stays (e.g., time of initiating nutritional support, mean energy intake, and mean protein intake). A secondary objective was to evaluate if mortality was affected by the delivery route (e.g., EN, PN, or both).

2. Material and methods

2.1. Study population

This multicenter prospective observational study was conducted at 38 ICUs across Spain between April and July 2018. Consecutive adult patients (age >18 years) needing artificial nutritional therapy for >48 h and staying in ICU for ≥72 h were included. We excluded patients admitted to ICU for postoperative recovery or ICU monitoring without needing specific therapy for organ support (e.g., vasopressors or non-invasive mechanical ventilation) and those able to be fed orally.

Patients in the present study were included from the Evaluation of Nutritional Practices in the Critical Care (ENPIC) study cohort. This research reflects a planned analysis and endpoint of this study (ClinicalTrials.gov Identifier: NCT03634943). The observational design meant that we made no attempt to influence general ICU care or the nutritional approach. However, to evaluate eligibility, participating hospitals were asked to provide information about their clinical nutrition practices and the degree of adherence to current guidelines (e.g., presence of a nutritional protocol or the involvement of a health care provider specializing in artificial nutritional support) [9].

2.2. Ethics

A central Institutional Ethics Committee (Comité d'Ètica i Assajos Clínics de Hospital Universitari de Bellvitge; Barcelona, Spain) approved the study (no. PR401/17), and the need for informed consent was waived due to the observational design.

2.3. Data collection and definitions

Data were extracted prospectively from the medical records of each patient and hosted in a centralized database for analysis (REDCap® electronic data at the Hospital Arnau de Vilanova, Lleida, Spain). The entered data were cleaned from August to November

2018, and data queries were sent back to the participating investigators for verification, after which we performed a second check and closed the database in May 2020. The following general data were collected: demographics; diagnoses and comorbidities; nutritional assessment, using the Subjective Global Assessment (SGA) and modified Nutrition Risk in the Critically Ill (mNUTRIC) scores (without the IL-6 component); and the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Simplified Acute Physiology Score (SAPS) II, and the Sequential Organ Failure Assessment (SOFA) score on ICU admission.

Details of nutritional therapy were also collected: the time nutritional therapy was initiated, the mean energy and protein intakes until ICU discharge or for a maximum of 14 days, and EN-related complications during their ICU stay (i.e., residual gastric volume, diarrhea, vomiting, aspiration, and mesenteric ischemia), as defined in the current literature [17]. Non-nutritional calories (dextrose infusion and propofol) were considered for the mean energy intake calculations. Enteral protein supplementation was also recorded for mean protein intake calculation.

Outcomes were recorded during ICU stays, including details of hemodynamic support, renal replacement therapies (RRT), mechanical ventilation, respiratory tract infection, and catheter-related infection. ICU and hospital mortality were followed-up for 28 days. The type of nutritional therapy was classified by the route of administration as either EN, PN, or both. The latter was classified into two subgroups based on the initial route of nutrition: EN-PN received EN initially and PN-EN received PN initially. The route was chosen by the treating medical ICU team based on the clinical indication.

To evaluate the estimate effect of different characteristics of nutrition therapy during ICU stay, we compared subgroups based on 28-day mortality. We also compared the differences among the different types of artificial nutritional therapies by administration route. The duration of nutritional therapy was included in all analysis to add a time perspective.

2.4. Statistical analyses

Data are expressed as means and standard deviations, median (interquartile ranges), or numbers and percentages, as appropriate. Analysis of variance was used to compare differences in characteristics between subgroups, and the Bonferroni post-hoc test was used to determine significant differences in the pairwise comparisons. The statistical analyses were conducted using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA), and two-tailed P-values <0.05 were considered statistically significant, unless stated otherwise.

The Mann–Whitney *U* test or the two-sample t-test were used to compare between groups, as appropriate, and the χ^2 test was used to evaluate categorical prognostic factors in the univariate analysis. In all cases, the Kolmogorov–Smirnov test and D'Agostino–Pearson omnibus normality test were used to check the normality of the population distribution. Survival analysis was conducted using the Kaplan–Meier estimator for each subgroup (log-rank test). Subsequent multivariate analysis was conducted using an adjusted multiple stepwise Cox regression analysis to assess the 28-day mortality. Variables were included in the initial model if they had a P-value <0.2 and were deemed suitable by the investigators based on careful consideration of confounding. Investigators selected variables based on current knowledge and

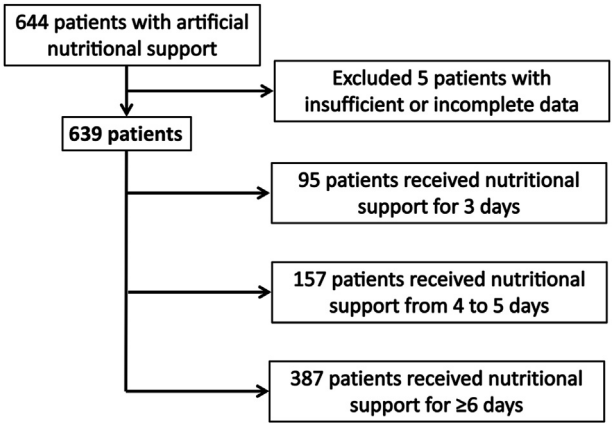

Fig. 1. Study flow chart.

Table 1
Characteristics, nutritional support, and outcomes of the patients admitted in the ICU population.

		All patients ($N = 639$)
Baseline characteristics & comorbidities		
Mean age (years)		61.8 ± 15
Sex (male)		432 (67.6%)
BMI ($kg \cdot m^{-2}$)		27.7 (27.4–28.4)
Hypertension		281 (44%)
Diabetes mellitus		164 (25.7%)
COPD		110 (17.2%)
AMI		94 (14.7%)
Chronic Liver Disease		32 (5%)
Chronic Renal Failure		68 (10.6%)
Immunosuppression		73 (11.4%)
Neoplasia		137 (21.4%)
Type of patient	Surgery	401 (62.8%)
	Medical	72 (11.2%)
	Trauma	166 (26%)
APACHE II		20 (14–25)
SAPS II		49 ± 17.7
SOFA (on admission)		7.1 ± 3.5
Patient with malnutrition (Based on SGA)		269 (42.2%)
mNUTRIC Score		4.2 ± 2.1
Patient at risk (Based on NUTRIC Score)		287 (46%)
Nutrition therapy		
Time of initiation of nutrition therapy (h)		28 (18–49)
Early EN (<48 h)		478 (74.8%)
Mean Kcal/kg/day [a]		15.7 (15.3–16.3)
Mean g protein/kg/day [a]		0.81 (0.79–0.84)
EN-related complications	Any complication	161 (30.8%)
	↑ GRV	81 (15.5%)
	Diarrhoea	51 (9.8%)
	Vomiting	8 (1.2%)
	Aspiration	1 (0.2%)
	Mesenteric ischemia	9 (1.7%)
Outcomes		
Mechanical ventilation		583 (91.2%)
Days on mechanical ventilation		13 (12–14)
Vasoactive drug support		474 (73.9%)
RRT needs		97 (15.1%)
Respiratory tract infection		166 (25.9%)
Catheter-related infections		42 (6.6%)
Mean ICU LOS (days)		13 (8–22)
Mean hospital LOS (days)		27 (16–45)
28-day Mortality		164 (25.6%)

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; AMI: Acute Myocardial Infarction; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SGA: Subjective Global Assessment; mNUTRIC: modified Nutrition Risk in the Critically Ill; EN: Enteral Nutrition; PN: Parenteral Nutrition; RRT: Renal Replacement Therapy; ICU: Intensive Care Unit; LOS: Length of stay. Results are expressed as mean ± standard deviation, percentage or median and interquartile range (first and third quartile).

[a] During the administration of the whole nutritional therapy or at least in the first 14 days of nutritional therapy.

Table 2
Differences in baseline characteristics, nutrition therapy, and outcomes based on the type of route.

		EN (63.4%; n = 405)	Total PN (18.2%; n = 116)	EN-PN (6.7%; n = 43)	PN-EN (11.7%; n = 75)	*p value*
Baseline characteristics & comorbidities						
Mean age (years)		60.8 ± 15	63.9 ± 14	60.2 ± 14	65.3 ± 13	***0.04***
Sex (male)		273 (67.4%)	72 (62.1%)	31 (72.1%)	56 (74.7%)	*0.29*
BMI ($kg \cdot m^{-2}$)		28.2 ± 6.3	27.1 ± 5.5	27.5 ± 5.4	26.3 ± 4.7	***0.04***
Hypertension		172 (42.5%)	55 (47.4%)	17 (39.5%)	37 (49.3%)	*0.54*
Diabetes mellitus		103 (25.4%)	28 (24.1%)	13 (30.2%)	20 (26.7%)	*0.88*
COPD		73 (18%)	15 (12.9%)	9 (20.9%)	13 (17.3%)	*0.55*
AMI		61 (15.1%)	17 (14.7%)	7 (16.3%)	9 (12%)	*0.90*
Chronic Liver Disease		22 (5.4%)	6 (5.2%)	0	4 (5.3%)	*0.48*
Chronic Renal Failure		42 (10.4%)	13 (11.2%)	3 (7%)	10 (13.3%)	*0.74*
Immunosuppression		42 (10.4%)	15 (12.9%)	6 (14%)	10 (13.3%)	*0.74*
Neoplasia		62 (15.3%)	45 (38.8%)	8 (18.6%)	22 (29.3%)	***<0.001***
Type of patient	Medical	289 (71.4%)	45 (38.8%)	31 (72.1%)	36 (48.2%)	***0.01***
	Trauma	60 (14.8%)	2 (1.7%)	4 (9.3%)	6 (8.2%)	***0.04***
	Surgery	56 (13.8%)	69 (59.5%)	8 (18.6%)	33 (44%)	*0.07*
APACHE II		20 (15–25)	19 (14–24)	20 (17–28)	20 (15–27)	***0.014***
SAPS II		48.3 ± 17.4	48 ± 19	52.1 ± 17.1	52.8 ± 17.3	*0.16*
SOFA (on admission)		7.1 ± 6.1	6.1 ± 4	8.7 ± 3.6	7.8 ± 3.8	***0.01***
Patient with malnutrition (based on SGA)		139 (34.4%)	68 (58.1%)	17 (39.5%)	45 (60%)	***<0.001***
mNUTRIC Score		3.9 ± 2.1	4.3 ± 1.9	4.9 ± 2.2	4.8 ± 1.8	***0.02***
Nutrition therapy						
Time of initiation of nutritional therapy (h)		28 (19–48)	28 (17–63)	41 (24–71)	24 (14–47)	*0.06*
Early EN (<48 h)		310 (76.8%)	83 (70.9%)	27 (61.4%)	58 (76.3%)	***0.11***
Days on nutrition therapy		8 (4–17)	5 (3–8)	12 (7–24)	9 (5–24)	***< 0.001***
Mean Kcal/kg/day [a]		15.4 ± 5.2	19.2 ± 7.3	14.4 ± 5.6	20.9 ± 5.7	***<0.001***
Mean g protein/kg/day [a]		0.75 ± 0.34	0.94 ± 0.43	0.81 ± 0.28	1.1 ± 0.35	***<0.001***
EN-related complications	Any complication	89 (21.9%)	NA	29 (67.4%)	32 (42.6%)	***<0.001***
	↑ GRV	46 (11.4%)	NA	16 (36.4%)	19 (25%)	***<0.001***
	Diarrhoea	35 (8.6%)	NA	8 (18.2%)	8 (10.5%)	***0.01***
	Vomiting	5 (1.2%)	NA	1 (2.3%)	2 (2.6%)	*0.59*
	Aspiration	0	NA	0	1 (1.3%)	*0.99*
	Mesenteric ischemia	3 (0.7%)	NA	4 (9.1%)	2 (2.6%)	***0.01***
Outcomes						
Mechanical ventilation		394 (97.5%)	79 (68.1%)	40 (93%)	70 (93%)	***<0.001***
Days on mechanical ventilation		13.2 ± 13.8	7.3 ± 11	21.5 ± 18.3	17.7 ± 21.3	***<0.001***
Vasoactive drug support		296 (73.3%)	75 (63.6%)	33 (75%)	70 (92.1%)	***<0.001***
RRT needs		41 (10.1%)	22 (18.6%)	18 (40.9%)	16 (21.1%)	***<0.001***
Respiratory tract infection		102 (25.2%)	35 (29.7%)	8 (18.2%)	21 (27.6%)	*0.48*
Catheter-related infections		26 (6.4%)	12 (10.2%)	2 (4.5%)	3 (3.9%)	*0.311*
Mean ICU stay (days)		13 (8–22)	8 (6–13)	16 (10–38)	16 (10–20)	***<0.001***
Mean hospital stay (days)		25 (16–42)	27 (15–47)	30 (17–54)	35 (19–62)	***0.012***
28-day Mortality		101 (24.9%)	27 (23.3%)	16 (37.2%)	20 ()	*0.19*

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; AMI: Acute Myocardial Infarction; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SGA: Subjective Global Assessment; mNUTRIC: modified Nutrition Risk in the Critically Ill; EN: Enteral Nutrition; PN: Parenteral Nutrition; RRT: Renal Replacement Therapy; ICU: Intensive Care Unit; NA: Not applicable. Results are expressed as mean ± standard deviation, percentage or median and interquartile range (first and third quartile). Significant p values are written in bold.

[a] During the administration of the whole nutritional therapy or at least in the first 14 days of nutritional therapy.

literature perspective (Additional File 1: Figure S1) [18]. We used the change-in-estimates criterion and backward deletion with a 10% cutoff to eliminate variables from the final model. To avoid destabilizing the multivariate analyses, we tested for interactions between all introduced variables. We then adjusted for age, patient type (e.g., medical, surgical, or trauma), illness severity (e.g., APACHE score), length of nutritional therapy, and data for which there were significant differences in baseline characteristics between subgroups. This helped to avoid confounders and the influence of illness severity when analyzing outcomes.

3. Results

Data for 644 patients were included during the study, but due to the exclusion criteria and cases with incomplete data, the final sample comprised 639 patients (see Fig. 1). Their baseline characteristics are shown in Table 1, together with details of any nutritional therapy and clinical outcomes. A small proportion (n = 18; 2.8%) of patients were underweight (Body Mass Index [BMI]<18.5 $kg\ m^{-2}$), 31% (n = 198) had normal BMI (BMI≥18.5–<25 $kg\ m^{-2}$), 39.1% (n = 250) had overweight (BMI≥25–<30 $kg\ m^{-2}$), 17.9% (n = 114) were obese type I (BMI≥30–<35 $kg\ m^{-2}$), 5.3% (n = 34) were obese type II (BMI≥35–<40 $kg\ m^{-2}$) and 3.9% (n = 25) were morbidly obese (BMI≥40 $kg\ m^{-2}$).

Nutritional therapy was given for a mean duration of 8 days (4–16 days). Only 95 patients (14.8%) received a short course (>48 h to <72 h) and only 157 (24.5%) received an intermediate course (>72 h to <7 days), whereas 387 (60.7%) received a long course (≥7 days). We showed differences among these subgroups in organ failure severity at admission; type, characteristics, and complications of nutritional support; and ICU outcomes (Additional file 2: Table S1). Patients who received a short course of nutritional therapy received PN more frequently (hazard ratio [HR]: 1.966; 95% Confidence Interval [CI]: 1.013–3.815; *P=0.046*) and exhibited lower 28-day mortality rates (HR: 0.458; 95% CI: 0.236–0.890; *P=0.021*).

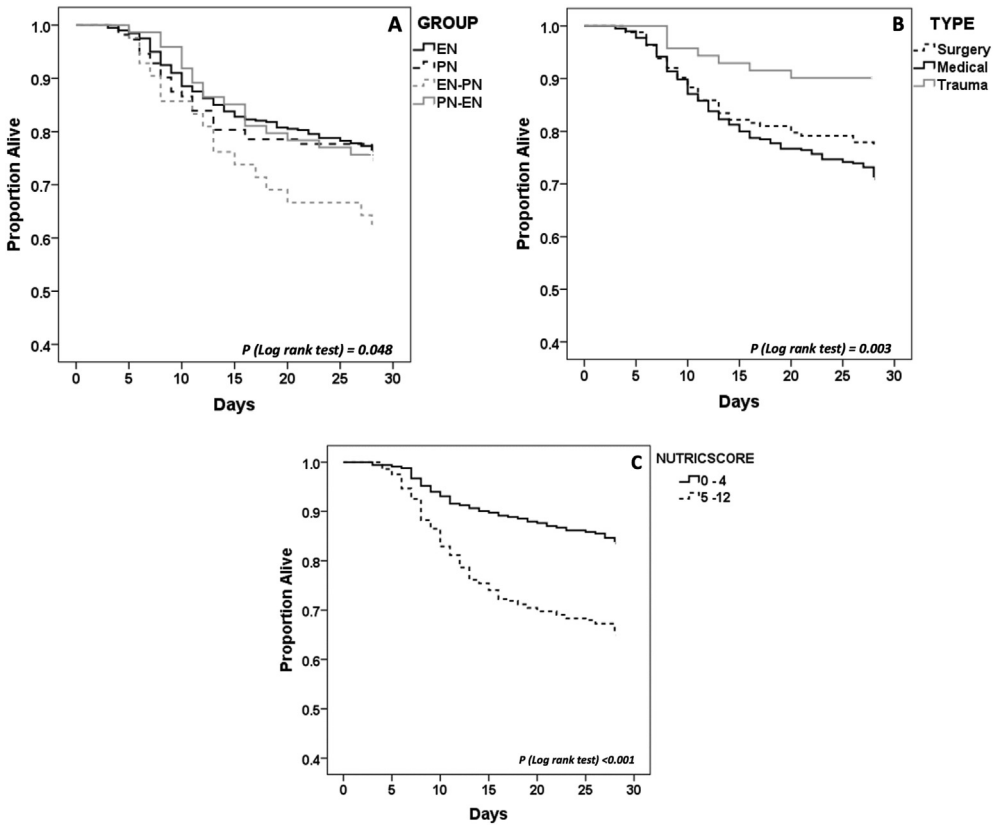

Fig. 2. Kaplan–Meier curves and log-rank test. The figures show survival by route of nutrition therapy (**A**), patient type (**B**), and nutritional risk (**C**). Nutritional risk was based on the modified Nutrition Risk in the Critically Ill (mNUTRIC) score.

We classified patients into four subgroups by route of nutritional therapy administration (Table 2). Overall, 118 patients (18.4%) received both EN and PN during ICU admission. Mesenteric ischemia was observed in 3 patients (2.5%) who received PN alone, and all 3 were related to surgical complications.

We found differences in illness severity (e.g., SOFA and APACHE II), patient characteristics, patient type, mean calories achieved, and mean protein achieved during and after nutritional support. Adjusting for length of nutritional support, ICU scores, and nutritional risk scores (i.e., NUTRIC and SGA) as confounding factors, we found differences between subgroups. Compared with the PN group, patients receiving EN were more likely to be admitted for a medical indication (HR: 5.564; 95% CI: 3.013–10.273; *P < 0.001*) and to require invasive mechanical ventilation compared with the PN subgroup (HR: 6.950; 95% CI: 1.120–7.766; *P < 0.001*).

Compared with the EN-PN subgroup, the EN subgroup performed better during early EN support (HR: 2.313; 95% CI: 1.130–4.763; *P=0.022*) and had fewer EN-related complications (HR: 0.264; 95% CI: 0.133–0.527; *P < 0.001*). Compared with PN-EN subgroup, the EN subgroup also needed less vasoactive drug support (HR: 0.234; 95% CI: 0.089–0.612; *P=0.003*) and suffered lower EN-related complication (HR: 0.469; 95% CI: 0.259–0.850; *P=0.013*). Compared with the EN-PN subgroup, the PN subgroup had a lower 28-day mortality rate (HR: 0.321; 95% CI: 0.134–0.335; *P=0.02*). Compared with the PN-EN subgroup, the EN-PN had more EN-related complications (HR: 2.983; 95% CI: 1.102–8.017; *P=0.032*) and higher 28-day mortality (HR: 3.149; 95% CI: 1.055–9.398; *P=0.04*). Indeed, the EN-PN subgroup showed the worst 28-day survival among all subgroups during ICU admission (Fig. 2A). Despite not achieving statistical significance, patients who received EN first line (i.e., the EN and EN-PN subgroups) received less mean calorie and protein delivery than patients in whom PN was started initially (i.e., the PN and PN-EN subgroups).

There were also differences between groups by survival, with non-survivors having more comorbidities and showing greater nutritional risk, illness severity, and need for RRT and vasopressor support (Table 3). Non-survivors also had a higher incidence of mesenteric ischemia and shorter ICU stays, whereas survivors received more protein and fewer calories while receiving nutritional support (or for 14 days). When we analyzed the 28-day survival, we found that patients admitted because of trauma (11.3%) showed a trend toward better survival than those admitted with either surgical (23.5%) or medical (29.4%) indications (*P=0.003*; Fig. 2B). Patients with higher nutritional risk also showed poorer survival, with survival rates of 87% and 68% for mNUTRIC scores of 0–4 and >4, respectively (*P < 0.001;* Fig. 2C). No analysis revealed an association by the time of starting nutritional therapy.

In the multivariate analysis, we adjusted for confounders such as the nutritional therapy duration, ICU score, patient type, and nutritional risk score (i.e., mNUTRIC and SGA). This revealed that older age and higher mNUTRIC and SOFA scores at ICU admission were positively associated with the 28-day mortality. The EN-PN subgroup also showed a positive association with 28-day mortality. A higher mean calorie delivery during nutritional therapy was associated with a higher mortality, whereas a higher mean protein delivery was protective against higher mortality (Table 4).

4. Discussion

The results of the present study have identified several nutritional - and nutritional-related - factors that may affect short-term mortality. Some of these factors, such as having a higher SOFA score

Table 3
Differences in baseline characteristics, nutrition therapy, and outcomes between survivors and non-survivors.

		Survivors (74.3%; n = 475)	Non-survivors[b] (25.6%; n = 164)	*p value*
Baseline characteristics & comorbidities				
Mean age (years)		59.8 ± 15	67.7 ± 12	***<0.001***
Sex (male)		325 (68.4%)	107 (65.2%)	*0.45*
BMI ($kg \cdot m^{-2}$)		27.8 (27.2–28.3)	27.1 (27.0–29.1)	*0.71*
Hypertension		194 (40.8%)	87 (53%)	***0.007***
Diabetes mellitus		118 (24.8%)	46 (28%)	*0.41*
COPD		68 (14.3%)	42 (25.6%)	***<0.001***
AMI		68 (14.3%)	26 (15.9%)	*0.63*
Chronic Liver Disease		23 (4.8%)	9 (5.5%)	*0.74*
Chronic Renal Failure		44 (9.3%)	24 (14.6%)	*0.05*
Immunosuppression		41 (8.6%)	32 (19.5%)	***<0.001***
Neoplasia		89 (18.7%)	48 (29.3%)	***0.005***
Type of patient	Medical	283 (59.6%)	118 (72%)	***0.04***
	Surgery	127 (26.7%)	39 (23.8%)	*0.15*
	Trauma	65 (13.7%)	7 (4.3%)	***0.001***
APACHE II		19 (14–24)	23 (17–27)	***<0.001***
SAPS II		47 ± 17	54 ± 18	***<0.001***
SOFA (on admission)		6.6 ± 3.3	8.4 ± 3.7	***<0.001***
Patient with malnutrition (based on SGA)		36.5% (173)	58.5% (96)	***<0.001***
mNUTRIC Score		3.8 ± 2.1	5.2 ± 1.7	***<0.001***
Patient at risk (based on NUTRIC)		39.7% (185)	64.6% (102)	***<0.001***
Nutrition therapy				
Time of initiation of nutritional therapy (h)		27 (18–48)	31 (20–50)	*0.23*
Type of nutritional support	EN	331 (69.7%)	117 (71.3%)	*0.85*
	PN	144 (30.3%)	47 (28.6%)	*0.75*
	EN-PN	27 (5.7%)	16 (9.8%)	*0.12*
	PN-EN	55 (11.6%)	20 (12.2%)	*0.91*
Early EN (<48 h)		357 (75.2%)	121 (73.8%)	*0.85*
Days on nutrition therapy		8 (4–18)	7 (4–12)	*0.17*
Mean kcal/kg/day [a]		15.6 (15.2–16.4)	15.9 (14.8–16.9)	*0.19*
Mean g protein/kg/day [a]		0.80 (0.78–0.85)	0.75 (0.72–0.85)	*0.12*
EN-related complications	Any complication	111 (23.3%)	39 (23.7%)	*0.83*
	↑ GRV	63 (16.3%)	18 (13.1%)	*0.41*
	Diarrhoea	40 (10.4%)	11 (8%)	*0.50*
	Vomiting	5 (1.3%)	3 (2%)	*0.98*
	Aspiration	1 (0.3%)	0	*0.99*
	Mesenteric ischemia	2 (0.5%)	7 (5.1%)	***0.002***
Outcomes				
Mechanical ventilation		430 (90.5%)	153 (93.3%)	*0.28*
Days on mechanical ventilation		13 (12–15)	12 (10–13)	*0.12*
Vasoactive drug support		337 (70.4%)	137 (83.5%)	***0.001***
RRT needs		59 (12.2%)	38 (23.2%)	***0.001***
Respiratory tract infection		124 (26.1%)	42 (25.6%)	*0.99*
Catheter-related infections		27 (5.9%)	15 (9.1%)	*0.15*
Mean ICU LOS (days)		13 (8–22)	11 (8–17)	***0.006***
Mean hospital LOS (days)		32 (19–54)	16 (10–27)	***<0.001***

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; AMI: Acute Myocardial Infarction; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SGA: Subjective Global Assessment; mNUTRIC: modified Nutrition Risk in the Critically Ill; EN: Enteral Nutrition; PN: Parenteral Nutrition; ↑ GRV: Elevated Gastric Residual Volume (>500 mL); RRT: Renal Replacement Therapy; ICU: Intensive Care Unit; LOS: Length of stay. Results are expressed as mean ± standard deviation, percentage or median and interquartile range (first and third quartile). Significant p values are written in bold.

[a] During the administration of the whole nutritional therapy or at least in the first 14 days of nutritional therapy.

[b] Based on 28-day mortality.

or higher age, are logically associated with mortality. However, the roles of the mNUTRIC score, the need for PN after starting EN, and a higher mean caloric intake during nutritional therapy associated with mortality, are findings that merit further discussion. The finding that a higher protein intake could be associated with lower mortality also warrants discussion.

The NUTRIC score was the first tool developed specifically to assess nutritional risk in patients admitted to ICU. It has been shown to correlate closely with poor outcomes [16,19], likely related to the inclusion of both age and the SOFA score [20]. Hospitalized older patients are certainly known to suffer more comorbidities, to be at nutritional risk, and to suffer malnutrition, which increase mortality [21]. The degree of organ failure is also linked directly to disease severity and the ability to tolerate nutritional therapy, with greater organ failure potentially causing gastrointestinal complications, gastrointestinal dysfunction and failure, and inadequate absorption, ultimately leading to malnutrition [22,23]. This latter issue is compounded by the inadequate provision of nutritional therapy during ICU admission, and perhaps most importantly, by excessive inflammation that may result in poorer nutrient absorption [24,25]. Thus, the association of age, the SOFA score, and the NUTRIC score with the 28-day mortality appears concordant with the pathophysiology of nutrition in critically ill patients.

The EN-PN subgroup was associated with higher 28-day mortality compared with the other subgroups. It is certainly plausible that the delay in starting PN, probably due to their clinical condition (i.e., higher severity) on ICU admission, contributed to the higher mortality rates. However, it is also plausible that these patients experienced higher rates of gastrointestinal dysfunction and failure

Table 4
Multivariate analysis* of factors associated with 28-day mortality in patients receiving artificial nutritional therapy during ICU stay.

	Hazard ratio (95% Confidence Interval)	*p value*
Age (years)	1.023 (1.008–1.038)	***0.003***
Non-trauma patient	1.965 (0.900–4.295)	*0.090*
SOFA Score	1.096 (1.036–1.160)	***0.001***
mNUTRIC Score	1.136 (1.025–1.259)	***0.015***
EN-PN subgroup	2.368 (1.168–4.798)	***0.017***
Mean Kcal/kg/day [a]	1.057 (1.015–1.101)	***0.008***
Mean g protein/kg/day [a]	0.507 (0.263–0.977)	***0.042***
Renal Replacement Therapy	1.742 (1.174–2.583)	*0.063*
Vasoactive drug support	1.564 (0.996–2.456)	*0.344*

*Model adjusted for potential confounders (i.e., age, patient type, illness severity, length of nutrition therapy, and other significant differences in baseline characteristics, such as sex, comorbidities, Body Mass Index, vasoactive drug support, and renal replacement therapy). SOFA: Sequential Organ Failure Assessment; mNUTRIC: modified Nutrition Risk in the Critically Ill; EN: Enteral Nutrition; PN: Parenteral Nutrition. Significant p values are written in bold.

[a] During the administration of the whole nutritional therapy or at least in the first 14 days of nutritional therapy.

[24]. We also showed, consistent with contemporary literature, that the use of PN is safe and it does not affect mortality directly [26]. In our cohort, patients receiving very short-term nutrition therapy were more likely to receive PN. This may be explained by the higher proportion of post-surgical patients and lower disease severity within this subgroup.

We also showed that calorie and protein goals, per recommended clinical practice guidelines, were not met in this study [2–4]. This was especially true of patients in whom EN was started from the beginning. Indeed, patients requiring PN after starting EN were more prone to EN-related complications, reflecting their disease severity and difficulty in achieving calorie and protein goals. The latter, together with lower calorie and protein delivery in the EN-PN subgroup, could be related to the higher mortality experienced by those patients. Recent contemporary trials have also reported that these goals were not achieved, with evidence that mean protein amounts of only 0.8–1.1 g kg^{-1} d^{-1} were delivered, possibly reflecting the difficulty inherent in providing nutritional therapy to patients with severe critical illnesses [10–13]. In addition, some guidelines claim for a lower caloric delivery (i.e., 11–14 kcal $kg^{-1} \cdot day^{-1}$) to obese patients, which represent a significant proportion (i.e., 27.1%) of our patients [27].

We found that higher mean caloric intake may be associated with 28-day mortality during at least the first two weeks of ICU admission: multivariable analysis showed us a higher 5.7% risk with each mean $Kcal \cdot Kg^{-1} \cdot day^{-1}$. This small effect combined with the caloric goals achieved in this study may seem controversial since the occurrence of complications has been associated with cumulated energy deficit in ICU patients [28]. However, the calorie goal for the critically ill is somewhat controversial given that permissive underfeeding (i.e., 60%–70% of the caloric target) appears to be not only safe but also superior in terms of outcomes in some ICU populations [29]. A full caloric target (i.e., 90%–100%) may not be the optimal in the early catabolic phase of an illness, and as such, the caloric target should be individualized based on the patient's nutritional reserve. A caloric intake closer to the target is recommended when there is a risk of malnutrition or when malnutrition and a poor nutritional reserve is present [30]. Most studies to date have also used formulas to calculate calorie goals and have not considered any non-nutritional calorie intake (e.g., glucose, citrate, or propofol), which is not the case of our study [31,32]. Thus, the association of a higher calorie intake with 28-day mortality is probably due to the high calorie goal in patients who needed lower caloric intakes, which may ultimately be associated with overfeeding.

Stress catabolism during the early phase of critical illness results in a loss of protein mass from muscle, contributes to sarcopenia, and ultimately leads to difficult recovery and poorer outcomes [30]. By contrast, a high-protein intake in the early phase of disease may decrease the acute negative protein balance and muscle loss while improving functional recovery [33]. Indeed, the increase in protein synthesis during the catabolic phase combined with adequate protein intake may help to reduce the negative protein balance [34]. This may explain our finding of improved survival with a higher mean protein intake during artificial nutritional therapy.

4.1. Limitations

Our study has several limitations, mainly related to its observational design, the heterogeneity of participants, and the difficulty in obtaining the correct macronutrient doses based on clinical practice guidelines during ICU admission. However, the multicenter nature, large sample size, clinical setting (reflecting real practice by ICU physicians delivering nutrition therapy), and long follow-up (14 days after ICU admission) are important strengths. Given the confounding influence of illness severity, patient type, and other potential confounders, we sought to account for these in our analyses. For example, this is important regarding the type of patient: trauma patients in our population experienced lower mortality, which may ultimately be explained by their characteristics (i.e., younger age, fewer comorbidities, and a better nutritional statuses). We also stratified patients by the type of artificial nutritional therapy to identify differences among the different routes. Our results regarding mean calorie and protein intakes come to the fore as areas that merit further analysis. We have an analysis planned to assess the adequacy of when macronutrient intake occurred. The novelty of this research is in the combination of all these methods together with all the combined reported observations in the multivariable analysis.

5. Conclusions

In summary, we showed that higher nutritional risk, greater organ failure severity, and older age are nutrition-related factors that may be associated with increased mortality. Regarding the type of nutritional therapy received, those patients needing PN after starting EN may represent a high mortality risk subgroup, probably due to greater illness severity and the presence of gastrointestinal failure, which also causes problems in giving appropriate nutritional therapy. Finally, we showed that higher mean protein intake and mean caloric intake during the first weeks of ICU stay may be associated with better and worst outcomes respectively. These findings, in turn, indicate that macronutrient delivery may have a prominent role in ICU outcomes.

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Conflict of interest

All the authors declare that they have no conflicts of interest in regard to the subject of this manuscript.

Authors' contributions

JCLD, TGC and LSG conceived, designed and coordinated the study. All authors collected the data during the study period and

participated in the revision. TGC, JCLD and JTC performed the statistical analysis and developed the first draft of the manuscript. All authors were involved in the interpretation of the results, critically revised the manuscript and approved the final version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.11.018.

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