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Predicting the outcome of artificial nutrition by clinical and functional indices

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Abstract

Objective: Artificial nutrition (AN) is now considered medical therapy and has progressively become one of the mainstays of the different therapeutic options available for home or hospitalized patients, including surgical, medical, and critically ill patients. The clinical relevance of any therapy is based on its efficacy and effectiveness and thus on the improvement of its cost efficiency, i.e., the ability to provide benefits to the patients with minimal wasting of human and financial resources. The aim of the present study was to identify those indices, clinical, functional, or nutritional, that may reliably predict, before the start of AN, those patients who are likely not to benefit from nutritional support.

Methods: Three hundred twelve clinical charts of patients receiving AN between January 1999 and September 2006 were retrospectively examined. Data registered before starting AN were collected and analyzed: general data (age, sex), clinical conditions (comorbidity, quality of life, frailty), anthropometric and biochemical indices, type of AN treatment (total enteral nutrition, total parenteral nutrition, mixed AN), and outcome of treatment.

Results: The percentage of negative outcomes (death or interruption of AN due to worsening clinical conditions within 10 d after starting AN) was meaningfully higher in subjects >80 y of age and with reduced social functions, higher comorbidity and/or frailty, reduced level of albumin, prealbumin, lymphocyte count, and cholinesterase and a higher level of C-reactive protein. The multivariate analysis showed that prealbumin and comorbidity were the best predictors of AN outcome. The logistic regression model with these variables showed a predictive value equal to 84.2%.

Conclusion: Proper prognostic instruments are necessary to perform optimal evaluations. The present study showed that a patient's general status (i.e., comorbidity, social quality of life, frailty) and nutritional and inflammatory statuses (i.e., lymphocyte count, albumin, prealbumin, C-reactive protein) have good predictive value on the effectiveness of AN.

Keywords: Artificial nutrition; Elderly; Nutritional status

Introduction

Artificial nutrition (AN) has progressively become one of the mainstays of the different therapeutic options available for home or hospitalized patients, including surgical, medical, and critically ill patients. Also, AN is now included among the tools representing the standard of care for patients with diseases requiring highly specialized therapies, i.e., hematologic patients undergoing bone marrow transplantation. Therefore, AN is now considered medical therapy [1]. The clinical relevance of any therapy, particularly in periods of shrinking resources for national health care systems, is based on its efficacy (i.e., the ability to significantly affect the clinical course of a given disease) and effectiveness (i.e., the ability to significantly affect the clinical course of a patient with that disease). Delivering AN with efficacy and effectiveness will enhance its cost effi-

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ciency, i.e., the ability to provide benefits to patients with minimal wasting of human and financial resources. In this light, the systematic use in clinical practice of indices identifying those patients who are not likely to benefit from AN should increase the efficiency of AN.

The reliability of different indices predicting the outcome of AN has been tested in a number of clinical studies, mainly involving patients with percutaneous endoscopic gastrostomy (PEG) [2–5]. However, these studies aimed at identifying those markers influencing clinically relevant parameters, i.e., long-term morbidity and mortality. By using this approach, the investigators assessed the efficacy of AN rather than its efficiency, which in turn received little attention. Also, these studies involved patients exclusively receiving total enteral nutrition, generally administered by PEG [2–8], or total parenteral nutrition (TPN) [9–11]. Therefore, the data obtained appear to pertain to specific groups of patients and cannot be extrapolated to the whole population. Further, some of the prognostic indices are detectable only when AN has been already started, i.e., when significant human and financial resources have been already committed.

We therefore designed the present study to identify those indices, clinical, functional, or nutritional, that may reliably predict, before starting AN, those patients who are likely not to benefit from nutritional support.

Materials and methods

Subjects

The study was approved by the local ethics committee. Clinical charts of patients receiving AN in the Clinical Rehabilitation Institute Villa delle Querce (Nemi, Rome, Italy) between January 1999 and September 2006 were retrospectively examined.

The following data registered before starting AN were collected from patients' charts. Clinical conditions were assessed by determining:

- The comorbidity index, as measured by the Individual Disease Severity scale [12]. This scale classifies comorbidities from 1 (asymptomatic) to 4 (terminal state, disease at extreme level of severity, disease unresponsive to therapy)
- Pressure sores, as assessed by the classification of Shea [13] (0, absence of lesions of degree $\leq$2; 1, presence of a single lesion or multiple lesions of degree 3 or 4)
- Biochemical parameters: hemoglobin, total cholesterol, cholinesterase, C-reactive protein (CRP), α_1-glycoprotein acid, albumin, transferrin, and lymphocyte count. The laboratory tests were performed at the laboratory of the Clinical Rehabilitation Institute Villa delle Querce. Peripheral venous blood was collected from the antecubital vein after an overnight fast. Serum concentrations of the biological indices were determined by routine methods with conventional commercial kits obtained from ABX Italia (Rome, Italy). Laboratory tests were carried out using a COBAS-MIRA analyzer and a Cell-Dyn 1700 Analyser (Abbott, Pomezia, Italy). The guidelines for the use of AN in adult patients of the Italian Society for Artificial Nutrition (SINPE) provided the standard values of the biological indices (albumin 3.5 g/L, transferrin 2.0 g/L, lymphocyte count 1500/mm^3) [1].
- Anthropometric parameters: midupper arm circumference (MAC) and triceps skinfold thickness (TSF). MAC was calculated from arm circumference (AC) and TSF: MAC (cm) = AC (cm) − ($\pi \times$ TSF [cm]).

The anthropometric measurements were performed according to the Standard Manual for Anthropometric Measures [14]. AC was measured to the nearest 0.1 cm with a cloth tape, and TSF to the nearest 0.2 mm with a Harpenden skinfold calliper (British Indicators Ltd., St. Albans, Herts, United Kingdom) on the dominant arm. The weighted mean of 10th percentile values for Italian samples enrolled in the Survey in Europe on Nutrition and the Elderly: a Concerted Action (SENECA) study were used as lower limits of normality for anthropometric parameters. These were defined as MAC values equal to 22 cm for men and 18.9 cm for women and TSF values equal to 5.2 mm for men and 9.7 mm for women [15].

Quality of life (QoL) was assessed by the use of Fletcher's [16] modified test:

- Social QoL (participation to social events, having contacts with family, etc.): 1, preserved and valid; 2, reduced; 3, impossible, absent
- Physical QoL (physical symptoms such as pain, suffering, malaise, nausea, vomiting): 1, absent; 2, bearable; 3, severe disturbance of QoL
- Psychological QoL: 1, positive attitude; 2, partially collaborative behavior; 3, deflection of mood, malaise sensation

Cognitive and functional statuses were determined by the use of the following tools:

- Cognitive status was assessed by the Short Portable Mental Status Questionnaire [17], a 10-item scale designed to evaluate the severity of cognitive impairment. The Short Portable Mental Status Questionnaire is designed to provide information in five areas of cognitive function: temporal and spatial orientations, personal memory, general knowledge, and concentration. Standards of performance established are intact mental functioning (zero to one mistake), borderline or mild cognitive impairment (two to three mistakes), definite but moderate cognitive impairment (four to six mistakes), and severe cognitive impairment (more than seven mistakes).

- Functional status was assessed according to the index of Katz et al. [18], which measures performance in self-care (feeding, bathing, dressing, continence) and mobility (transfers to the toilet, ambulation). Severity of limitations in activities of daily living (ADLs) was calculated by adding up the weighted levels of the six ADLs (graded from 2, "no disability," to 0, "can't perform the ADL with equipment or personal assistance").

Frailty was assessed by using the evaluation tool of Trabucchi et al. [19], which considers age, cognitive functions, and functional and nutritional statuses. For each item, three levels were identified: age (<75, 75–80, >80 y), cognitive functions (normal, mildly impaired, severely impaired), functional status (independent, dependent in one to two ADLs, dependent in more than two ADLs), and nutritional status (albumin level >35, 30–35, <30 g/L). A frailty score was assigned to each level: 0 point for best scenarios (age <75 y, normal cognitive functions) and up to 2 points for worst scenarios (age >80 y, severely impaired cognitive functions). Frailty classes were defined as class A (0–2 points), class B (3–4 points) and class C (5–8 points).

The prescription of nutritional support and its monitoring were in accordance with national and international guidelines [1,20]. Enteral and parenteral nutrition were always delivered by infusional pumps. Nutritional support was delivered by enteral access (nasogastric tube, PEG) and/or parenteral access (central venous catheter, port or peripherally inserted central catheter).

The following data, regarding the interruption of nutritional support of patients enrolled, were collected from clinical records: treatment duration and reason for interruption (1, death; 2, weaning; 3, refuse; 4, transfer to other hospitals or clinics; 5, demission; 6, interruptions due to worsening clinical condition).

To meet the aims of the present study, treatment outcome was judged in terms of efficiency: positive in all cases in which weaning was possible or AN was interrupted (because of a patient's death, worsening clinical status, demission, or transfer) after day 30 of treatment or negative in all cases in which death or interruption due to a worsening clinical condition occurred within the initial 10 d of treatment.

Data analysis

The outcome of AN was considered 0 when negative and 1 when positive, as previously specified. The independent variables (baseline functional, cognitive, clinical, and nutritional statuses) were also coded as presented in Table 1.

Table 1
Independent variables coding

	Codes				
	0	1	2	3	4
Cancer	Absence of anamnesis	Presence of anamnesis			
Pressure sores	Absence or presence of ulcers of degree 1–2	Presence of ≥1 lesion of degree 3–4			
TSF (mm)	≥5.2 for men/9.7 for women	<5.2 for men/9.7 for women			
MAC (cm)	≥22 for men/18.9 for women	<22 for men/18.9 for women			
Hemoglobin (g/dL)	>12	≤12			
α_1-Glycoprotein acid (mg/dL)	<160	≥160			
Age (y)	<75	75–80	>80		
Lymphocyte count/mm^3	>1500	1500–1200	<1200		
Transferrin (mg/dL)	>200	200–150	<150		
CRP (mg/dL)	<7	7–20	>20		
Albumin (g/L)	>35	31–35	<31		
Cognitive status	Unimpaired/mildly deteriorated	Moderately deteriorated	Severely deteriorated		
Frailty		Class A = 0–2 points	Class B = 3–4 points	Class C = 5–8 points	
Social QoL		Preserved and valid	Reduced	Impossible, absent	
Physiologic QoL		Positive attitude	Partially collaborative attitude	Deflection of mood, malaise sensation	
Physical QoL		Preserved and valid	Bearable	Severe disturbance of QoL	
Comorbidity		Asymptomatic	Light or moderate; symptoms responding to therapy	Severe and not completely responding to therapy	Terminal status, disease at extreme level of severity and not responding to therapy

CRP, C-reactive protein; MAC, midupper arm circumference; QoL, quality of life; TSF, triceps skinfold thickness

Univariate analysis (*t* test, chi-square test) assessed the relation between independent and outcome variables. The relative risk and 95% confidence interval for the association of tested variables with the outcome variables were calculated. Variables with proven univariate correlation with the outcome were entered into a pool of potential contributors in the logistic regression analysis. The models were statistically evaluated using a block model, where all variables were included, and a forward likelihood stepwise method (cutoff probability for entry 0.05). With each added variable, the discriminant function was recalculated, and any variable that no longer met the significance level was removed from the equation (cutoff probability for removal 0.1).

To assess how our models fit, we compared our predictions with the outcomes observed in the subjects with a predicted probability ≥0.5 (overall percentage of correct classification, sensitivity, specificity, positive and negative predictive values) and examined how "likely" the sample results actually were (given the parameter estimates). Because the likelihood is a small number (<1), it is customary to use −2 times the log of likelihood (−2LL) as a measurement of how well the estimated model fits the data. Changes in the likelihood value were used to determine how the fit of a model changes as variables are added or deleted from it.

Moreover, the area under the receiver operating characteristic curve was calculated. This is the graphic picture of sensitivity (probability to complete a type 1 error; false negative) regarding the complement to 1 of the specificity (estimate of the probability to complete a type 2 error; false positive) of the logistic model to change the level of decisional threshold. The curve with ideal values of specificity and sensitivity that are more close together has the course to the advanced side. The subtended area to such a curve represents the probability that a subject is classified correctly from the logistic model and must have a value >0.5.

Data were analyzed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA, 1989–1999) and Win Episcope 2.0 (Facultad de Veterinaria di Saragozza, Saragozza, Italy; Wageningen University, Wageningen, Netherlands; University of Edinburgh, Edinburgh, United Kingdom).

Results

Sample description

The sample studied includes all 312 patients receiving AN from January 1999 to September 2006: 181 women (58% of total sample, 77 ± 12 y of age age) and 131 men (42% of total sample, 69 ± 17 y of age).

The main characteristics of the examined sample are listed in Table 2. In particular, 37.2% of the sample, at the moment of AN onset, was older than 80 y. QoL was characterized by a reduction or absence of social function in 84% of the sample. Moreover, clinical symptoms determined a serious disturbance of QoL in 38% of the sample. Depression was present in 40% of the patients.

Table 2
General characteristics of the sample

	All patients (%)	Male (%)	Female (%)
Age (y)*			
<75	40.8	50	34.2
75–80	22.3	25.4	20.1
>80	36.9	24.6	45.7
Quality of life			
Social			
Preserved	15.4	19.2	12.5
Mediocre	35.8	37.5	34.6
Absent	48.8	43.3	52.9
Physical (symptoms)*			
Absent	2.9	6.8	0
Bearable	37.4	33	40.7
Severe disturbance of quality of life	43.7	39.8	46.7
Not assessable	16	20.4	12.6
Psychological			
Positive attitude	22.6	22.9	22.2
Partially co-operative attitude	37.6	43.8	31.1
Deflected mood	39.8	33.3	46.7

* $P < 0.05$.

Table 3 presents the clinical characteristics of the sample. More than 85% of the sample was dependent in more than two ADL functions and cognitive status was seriously deteriorated in 69% of cases. A high level of frailty (class C) was present in 53.5% of the sample.

As regards clinical status, 44% of cases presented a symptomatology only partially responding to the treatment, whereas 50.5% of patients were characterized by a disease at an extreme level of severity that was unresponsive to therapy. In particular, the presence of cancer was found in 11.5% of patients and pressure sores (stage 3 or 4) were present in 37.5% of the sample.

Motivations that more frequently lead to AN were dysphagia (50.5%) and insufficient feeding negatively conditioning nutritional status (44.5%).

Total enteral nutrition was performed in 57% of cases, TPN in 30%, and "mixed" AN (total enteral nutrition plus TPN) in 13% of the sample. The access methods more frequently used were nasogastric tubes (52%), PEGs (12%), and central venous catheters (23%).

According to these defined criteria, AN interventions had a positive outcome in 62.6% of cases.

Univariate analysis

The percentage of negative outcomes was higher in subjects older than 80 y (52.2% versus 29.2%; chi-square = 11.7, $P = 0.003$).

A good correlation was found between the level of social functions and the outcome of AN: negative outcome was

Table 3
Clinical status characteristics

	All patients (%)	Male (%)	Female (%)
Frailty			
Autonomy			
No function lost	4.9	2.9	6.4
Up to 2 functions lost	8.6	12.5	5.7
>2 functions in activities of daily living	86.5	84.6	87.9
Cognitive status			
Normal	14.8	17.3	12.9
Moderate impairment	17.2	22.1	13.6
Severe impairment	68	60.6	73.6
Class C*	54.1	47.7	58.5
Clinical status			
Comorbidity: severe symptoms, not completely responding to therapy (classes 3–4)	94.7	94.3	95
Cancer	14.3	17.1	12.2
Pressure sores (degree 3 or 4)	36.7	31.2	40.6
TSF (<5.2 mm for men/9.7 mm for women)	15	11	18.3
MAC (<22 cm for men/18.9 cm for women)	54.1	60	49.2
CRP (>20 mg/dL)	73.8	78.8	69.6
Lymphocyte count (<1500/mm^3)	39.3	37.1	40.9
Transferrin (<200 mg/dL)	76.9	80.2	74.1
Albumin (<35 g/L)*	72.8	64.6	78.9
Hemoglobin (≤12 g/dL)*	41.5	49.5	35.8

CRP, C-reactive protein; MAC, midupper arm circumference; TSF, triceps skinfold thickness
* $P < 0.05$.

more frequent when social function was reduced or absent (37.9% or 39.8%, respectively, versus 11.1%; chi-square = 7.9, $P = 0.019$).

Only a sure tendency ($P = 0.089$) and no correlation ($P = 0.335$) were found for physical function parameters of QoL and psychological status, respectively, in determining the outcome of AN. As regards cognitive state, the subjects with severe cognitive impairment had more frequently a negative outcome for AN (39.5% versus 16.7%; chi-square = 6.2, $P = 0.046$).

Comorbidity (level 3 or 4) also influenced the outcome of AN (25.3% and 46.5%, respectively, versus 0%; chi-square = 14.3, $P = 0.001$).

Frailty class C more frequently induced a negative outcome for AN (42.8% versus 30.3%; chi-square = 14.3, $P = 0.001$).

A correlation with the outcome of AN was not found for psychological state ($P = 0.335$), dependency in ADLs ($P = 0.1$), presence of cancer ($P = 0.969$), or pressure sores ($P = 0.543$).

A statistically significant correlation was found for albumin, CRP, and lymphocyte count.

Albumin

A negative outcome was present in 24%, 23%, and 43.5% of the sample for normal (35 g/L), light (31–35 g/L), and severe (<31 g/L) reductions of albumin values, respectively (chi-square = 7.5, $P = 0.024$). The mean value of albumin was different according to AN outcome: 30.2 ± 6 versus 33 ± 6 g/L for negative versus positive outcome, respectively ($P = 0.008$).

C-reactive protein

A negative outcome was present in 10.7%, 16.6%, and 35.2% of subjects with normal (<7 mg/dL), increased (7–20 mg/dL), and higher (>20 mg/dL) levels, respectively (chi-square = 6.7, $P = 0.035$). The mean CRP values were 135.2 ± 251 mg/dL for negative outcome and 52.9 ± 48 mg/dL for positive outcome ($P = 0.003$).

Lymphocyte count

Lymphocyte count was correlated with negative outcome; more frequently (44.4%), this outcome was present in subjects with lower lymphocyte counts (≤1500/mm^3) than in subjects with normal values (25%; chi-square = 11.7, $P = 0.030$).

Moreover, prealbumin and cholinesterase levels were different in positive outcome compared with negative outcome: 19.1 ± 8 versus 12.3 ± 6 mg/L for prealbumin ($P = 0.003$) and 4550 ± 2068 versus 3596 ± 2199 U/L ($P = 0.011$) for cholinesterase (Table 4).

Values for TSF ($P = 0.931$), MAC ($P = 0.409$), hemoglobin ($P = 0.956$), transferrin ($P = 0.708$), α_1-glycoprotein acid ($P = 0.746$), and total cholesterol ($P = 0.083$) were not correlated with AN outcome.

Multivariate analysis

The multivariate analysis was performed using only the independent variables significantly correlated with AN outcome in the univariate analysis: comorbidity, QoL, frailty, lymphocyte count, CRP, prealbumin, and cholinesterase (Table 4).

Although a significant correlation was found in the univariate analysis for albumin, cognitive status, and age, these were excluded from the multivariate analysis because they were already considered in the frailty definition.

In the block model of the logistic regression analysis, all the selected variables were included. The predictive value of the model was 89.7% (specificity 97.7%, sensitivity 64.3%, predictive positive value 90%, and predictive negative value 89.6%). The area under the receiver operating characteristic curve (equal to 0.851) confirmed the validity of the model.

With the forward stepwise analysis, only prealbumin and comorbidity were considered in the final model. In this case the predictive value of the model was 84.2% (specificity 95%, sensitivity 50%, positive predictive value 77.8%, and negative predictive value 85.4%). In this case, too, the area under the receiver operating characteristic curve (equal to 0.801) confirmed the validity of the regression model.

Table 4
Artificial nutrition outcome—logistic regression analysis

Model	Predictive value					−2LL*	R^2		Area under ROC curve†
	Overall predictive value	Sensitivity	Specificity	PPV	NPV		Cox-Snell	Nagelkerke	
Block model (comorbidity, social-quality of life, frailty classes, lymphocyte count, CRP, prealbumin, cholinesterase)	89.7	64.3	97.7	90	89.6	42.5	0.311	0.464	0.851 ± 0.065 (0.724–0.977)
Forward stepwise selection (prealbumin, comorbidity)	84.2	50.0	95.3	77.8	85.4	47.7	0.243	0.362	0.801 ± 0.057 (0.689–0.913)

−2LL, −2 log likelihood; CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characteristic
* Initial −2LL = 52.8.
† Mean ± SE (95% confidence interval).

The −2LL values of both models (42.5 and 47.7, respectively) were smaller than the initial −2LL value (52.8), confirming the validity of the regression models.

Discussion

The main findings of the present study are the demonstration that the assessment of a patient's general status (i.e., comorbidity, social QoL, frailty) and nutritional and inflammatory statuses (i.e., lymphocyte count, albumin, prealbumin, CRP) before AN is started reliably predicts the outcome of AN.

For the purposes of this study, weaning from AN or AN longer than 30 d was considered a positive outcome. Although the most recent guidelines indicate that a period of AN shorter than 7–10 d has no impact on a patient's nutritional and metabolic statuses, we considered a much longer threshold because 30 d represents an adequate interval to obtain significant modifications of a number of clinical parameters (i.e., albumin, anthropometric indices) positively influencing outcome, particularly in geriatric patients. The 30-d limit appears to be not too short an interval even if the recent literature considers mortality ranging from 30 d [3–6,9,10] up to 1–2 y [2,7,11,21] an index of negative outcome. We believe that such a long period of AN is inappropriate to assess its efficiency, because AN is generally provided to patients with severe illness, as is the case of the population enrolled in our study showing a large prevalence (>90%) of patients with a comorbidity index of 3 or 4. In this population, any death occurring 1 or 2 y after starting AN may be secondary to causes not related to the nutritional support the patient was receiving and therefore cannot be used to assess its efficacy.

Death or interruption of AN without weaning, occurring within 10 d from the start of AN, was considered a negative outcome. By setting these criteria, the cases in which AN could not influence the metabolic and nutritional statuses of the patients, thus representing a waste of human and financial resources, were identified.

Our study shows that worsening of cognitive function, severe comorbidity, and poor social interaction represent variables significantly correlated with an increased incidence of death or interruption of AN within 10 d from its start. Therefore, comorbidity, cognitive function, and social function may well represent a patient's general status.

Sixty-nine percent of patients showed severe cognitive impairment. Although there are many data supporting the decision not to use AN in these patients [2], the decision to with-hold or withdraw AN in these subjects represents a controversy in clinical nutrition. Religious beliefs and relatives' considerations and expectations make the decision difficult. Our data confirm the uselessness of AN in severe cognitive impairment.

Comorbidity was previously identified as a reliable predictive marker of survival, length of hospital stay, and

complication rate [22,23]. Also, a correlation has been shown between the comorbidity index and outcome of AN, indicating an increased death rate at 30 d in patients undergoing PEG placement [3,6] or at 6 mo in patients receiving enteral nutrition [2].

Previous studies have shown that the severity of the clinical status of any patient does not result from the mere addition of patients' different diseases, but rather from the interaction and reciprocal influence that each disease exerts over the other, eventually determining severity and outcome. Furthermore, each patient has a specific and unique ability to respond to the disease and to the treatment, which is in turn influenced by that patient's general status, i.e., physical, psychological, and social functions [24,25]. Supporting this evidence, significant correlations have been found between survival after initiation of nutritional support and Acute Physiology and Chronic Health Evaluation II score [21] and between mortality within 30 d from PEG placement and Global Norton Scale, i.e., an index used to assess the risk of developing pressure ulcers and based on the evaluation of a patient's physical and cognitive parameters, i.e., general status [4].

The influence of clinical general status on patients' outcome is of particular importance in the geriatric population, which is characterized by frailty and thus by the predisposition to the failure of the clinical homeostasis and the inability to recover from the failure [26–32]. In our present study and in other previous experiences [24,25], frailty has been assessed by the index proposed by Trabucchi et al., which encompasses age, cognitive and functional statuses, and nutritional status. The results show that frailty is significantly related to the outcome of AN, i.e., more negative outcomes were found in patients with more severe frailty.

To support this approach, the influence of age and albumin levels were separately analyzed, showing that an age >80 y and low albumin levels correlate with a higher proportion of AN failure. The role of AN in age is controversial. Although some studies found no relation between age and mortality at 30 d after PEG placement [3,4], there are reports indicating the existence of a causative relation [7]. Conceptually, age should be related to the patients' prognosis and the outcome of AN, considering that it is the main determinant of frailty [19,30].

Although our population was characterized by an advanced mean age and most of the patients were older than 65 y, the results of our study fit well for the subgroup of subjects younger than 65 y. In these patients the same variables are able to predict the outcome of AN.

The role of albuminemia is more complex, because albumin levels are a marker of not only nutritional status but also of inflammatory process and liver failure. Several studies have shown that hypoalbuminemia is related to increased mortality at 30 d [5,33–35] and 6 mo [8] after PEG placement and in patients receiving TPN [5,7] or no nutritional support [36–42]. However, data exist showing no role of albumin levels in mortality, particularly in patients with PEG [3,4,35,43]. In our study, albumin levels <31 g/L were significantly related to increased mortality or discontinuation of AN within 10 d from its start. These data strengthen the importance of albuminemia as a marker of nutritional status and, more generally, of a patient's clinical condition.

In our study, prealbumin levels were significantly correlated with negative outcome. Prealbumin, whose half-life is much shorter than that of albumin (2–3 versus 21 d) is widely acknowledged as a marker of nutritional status, its concentrations being reduced by malnutrition, but also by inflammation and liver diseases. Clinical data investigating the influence of prealbumin on the outcome of AN are scanty. Lim et al. [44] found no significant relation between rising prealbumin levels in patients receiving protein supplementation and reduced mortality [44]. Similarly, no relation was found between reduced mortality at 6 mo and rising prealbumin levels in patients receiving enteral nutrition [2].

The role of total lymphocyte count and transferrin levels on the outcome of AN has received little consideration so far. No data are available for total lymphocyte count, whereas plasma transferrin levels were found to correlate to survival in patients receiving TPN [9]. Our study shows that low transferrin levels do not relate to an increased incidence of negative outcome within the first 10 d of treatment. In contrast, reduced total lymphocyte count is significantly associated with the failure of AN, suggesting that this marker encompasses information not only on a patient's nutritional status but also on that patient's resistance to infection.

High levels of CRP (>20 mg/L) have been found more frequently in patients in whom AN has failed. This result was expected considering that CRP is a marker of inflammatory status, which may well worsen a patient's clinical condition and thus facilitate the occurrence of complications. Similarly to CRP, α_1-glycoprotein is widely considered an acute-phase protein. However, our study could not demonstrate any significant correlation between α_1-glycoprotein and the outcome of AN. These apparently discordant results could be explained by the different half-lives of the two proteins: whereas CRP levels rise shortly after the inflammatory insult, peaks after 2–3 d, and is related to the tissue damage, α_1-glycoprotein levels react more slowly and are related to the general stress condition of the patient. Therefore, any inflammatory conditions occurring within 48 h before the start of AN may influence the outcome of the nutritional support, while earlier insults do not appear to exert any role.

The relation existing between plasma proteins (carrier or acute-phase proteins) has been confirmed by the studies assessing the role of the Prognostic Inflammatory and Nutritional Index [45,46], which have been summarized by Fuhrman et al. [47]. Indeed, albumin, prealbumin, and transferrin plasma levels should be better considered as "negative" acute-phase proteins, i.e., their circulating levels

decrease in the presence of an inflammatory status. In this light, these proteins are not direct markers of nutritional status, but only indirect indices because they reflect cytokine-induced stress, catabolism, and anorexia, which in turn affect a patient's nutritional status. Bearing this in mind, it appears critical that the presence of inflammatory status should be carefully evaluated before starting any nutritional support, because inflammation may negatively influence the outcome of AN, thereby requiring more careful monitoring and perhaps a nutraceutical approach with immunomodulating nutrients.

The clinical indices that in our study were found significantly related to the failure of AN have been further validated by the multivariate analysis, block analysis, or stepwise analysis, which showed that the model based on the inclusion of only two parameters, i.e., prealbumin and comorbidity, has a highly significant predictive value and specificity.

Anthropometric parameters (MAC and TSF) were not correlated with the outcome of AN, although they are useful in clinical practice for the evaluation of nutritional status before and during AN. They are probably not sufficiently sensitive in perceiving rapid modifications of clinical-nutritional-inflammatory status. We had little information, not sufficient to be correctly analyzed, on changing body mass index or unvoluntary weight loss, due probably to the cognitive impairment of our patients.

It is acknowledged that to better assess our present data, some potential limitations should be considered. The present study is based on a retrospective analysis of case-report forms originally conducted for other purposes. The population studied is based on inpatients of the Clinical Rehabilitative Institute Villa delle Querce, and includes patients admitted to different rehabilitation wards (cardiologic, pulmonary diseases, metabolic-nutritional), a nursing home, the awakening unit, and the intensive care unit. Consequently, the cases analyzed mainly deal with elderly patients with chronic diseases, although the predictive models well fit even for younger subjects included in the studied population.

Another limit of the study is that, at present, our results do not lead to concise decision aids for daily practice. Further studies must be performed to clearly define a flow-chart helping physicians in the decision of carrying out AN or not.

Conclusion

Nutritional feeding support should be considered as a real therapeutic treatment, in addition to other vital support therapies. Costs and benefits (as patient nutritional status and/or clinical improvement) should be well evaluated for each patient (QoL, complications) or, in economics terms, for the entire community.

At present, internationally accepted and codified guidelines for appropriate prescription of nutritional feeding do not exist. This implies that, in these cases, it is difficult for physicians to choose whether or not to use nutritional feeding in the treatment of particular geriatric patients or those affected by severe chronic pathology.

In our opinion, to make the better choice, the following considerations are essential:

1. An accurate clinical-nutritional evaluation of patients with respect to their psychophysical status and QoL
2. A nutritional feeding planning resulting from the collective decision of various professionals involved (general doctor or physician, dietitian and nurse, patient and relatives) so that a multidisciplinary approach and different position comparisons may lead to the most objective possible choice
3. Check and a constant quest for quality directed to revise decisions on the basis of new information regarding the evolution of the case

Proper prognostic instruments are necessary to perform optimal evaluations. The present study shows that a patient's general status (i.e., comorbidity, social QoL, frailty), nutritional and inflammatory statuses (i.e., lymphocyte count, albumin, prealbumin, CRP) have a good predictive value on the effectiveness of AN.

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