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Prevalence and Clinical Outcome Associated with Preexisting Malnutrition in Acute Renal Failure: A Prospective Cohort Study

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Abstract. Malnutrition is a frequent finding in hospitalized patients and is associated with an increased risk of subsequent in-hospital morbidity and mortality. Both prevalence and prognostic relevance of preexisting malnutrition in patients referred to nephrology wards for acute renal failure (ARF) are still unknown. This study tests the hypothesis that malnutrition is frequent in such clinical setting, and is associated with excess in-hospital morbidity and mortality. A prospective cohort of 309 patients admitted to a renal intermediate care unit during a 42-mo period with ARF diagnosis was studied. Patients with malnutrition were identified at admission by the Subjective Global Assessment of nutritional status method (SGA); nutritional status was also evaluated by anthropometric, biochemical, and immunologic parameters. Outcome measures included in-hospital mortality and morbidity, and use of health care resources. In-hospital mortality was 39% (120 of 309); renal replacement therapies (hemodialysis or continuous hemofiltration) were performed in 67% of patients (206 of 309); APACHE II score was 23.1 ± 8.2 (range, 10 to 52). Severe malnutrition by SGA was found in 42% of patients with ARF; anthropometric, biochemical, and immunologic nutritional indexes were significantly reduced in this group compared with patients with normal nutritional status. Severely malnourished patients, as compared to patients with normal nutritional status, had significantly increased morbidity for sepsis (odds ratio [OR] 2.88; 95% confidence interval [CI], 1.53 to 5.42, $P < 0.001$), septic shock (OR 4.05; 95% CI, 1.46 to 11.28, $P < 0.01$), hemorrhage (OR 2.98; 95% CI, 1.45 to 6.13, $P < 0.01$), intestinal occlusion (OR 5.57; 95% CI, 1.57 to 19.74, $P < 0.01$), cardiac dysrhythmia (OR 2.29; 95% CI, 1.36 to 3.85, $P < 0.01$), cardiogenic shock (OR 4.39; 95% CI, 1.83 to 10.55, $P < .001$), and acute respiratory failure with mechanical ventilation need (OR 3.35; 95% CI, 3.35 to 8.74, $P < 0.0.5$). Hospital length of stay was significantly increased ($P < 0.01$), and the presence of severe malnutrition was associated with a significant increase of in-hospital mortality (OR 7.21; 95% CI, 4.08 to 12.73, $P < 0.001$). Preexisting malnutrition was a statistically significant, independent predictor of in-hospital mortality at multivariable logistic regression analysis both with comorbidities (OR 2.02; 95% CI, 1.50 to 2.71, $P < 0.001$), and with comorbidities and complications (OR 2.12; 95% CI, 1.61 to 2.89, $P < 0.001$). Malnutrition is highly prevalent among ARF patients and increases the likelihood of in-hospital death, complications, and use of health care resources.

Major advances in the diagnosis and treatment of acute renal failure (ARF) have been made over the past few years, yet prognosis of the syndrome remains poor, as the patients are now increasingly older, more severely ill, have more chronic comorbidities, and an increased number of conditions contributing to ARF development (1–4). Many factors of potential prognostic value have been identified in ARF patients (underlying malignancy, previously altered health status, length of hospitalization before the ARF episode, delayed occurrence of ARF, sepsis, oliguria, severity of illness, etc.) (3–8); although malnutrition is highly prevalent among hospitalized patients (9–11), and is well known as a negative prognostic factor (12–21), no mention of nutritional status is usually made in studies on ARF patient outcome. Moreover, several controlled studies in the past tried to evaluate the effects of nutritional support on ARF patient mortality, with no clear-cut results (22–26), but again no attention was paid to the presence and possible role of previous malnutrition. We thought that if preexisting malnutrition is a frequent finding in ARF patients, and is associated with an increased risk of morbidity and mortality, nutritional status evaluation in this clinical condition would allow the definition of an important variable for patient risk stratification at the time of referral to specialized units (nephrology units or intensive care units). Thus, we designed the present prospective cohort study to: (*1*) investigate the

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Table 1. Demographic and clinical data of the ARF patient cohort[a]

No. of patients	309
Age (yr)	67 ± 15 (18 to 93)
Gender	197 M (64%), 112 F (36%)
Location	
emergency room	31 (10%)
medical wards	177 (57%)
coronary care unit	8 (3%)
surgical wards	46 (15%)
surgical ICU	19 (6%)
trauma ICU	13 (4%)
heart surgery ICU	15 (5%)
Medical ARF	227 (73%)
Surgical ARF	82 (27%)
Serum creatinine (mg/dl)	5.9 ± 3.7 (2 to 23)
BUN (mg/dl)	93.7 ± 48.5 (37 to 322)
Oliguria	204 (66%)
Renal replacement therapy (hemodialysis or CRRT)	206 (67%)
No. of patients on hemodialysis	172 (57%)
Hemodialysis sessions (per patient)	6.9 ± 8.3 (1 to 48; median 4)
CRRT (patients)	34 (11%)
CRRT hours/patient	77 ± 49 (15 to 240; median 72)
APACHE II score	23.1 ± 8.2 (10 to 52)
In-hospital mortality	120 (39%)

[a] ARF, acute renal failure; ICU, intensive care unit; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.
To convert the value for BUN to milliequivalent per liter, multiply by 0.357. To convert the value for serum creatinine to micromoles per liter, multiply by 88.4.

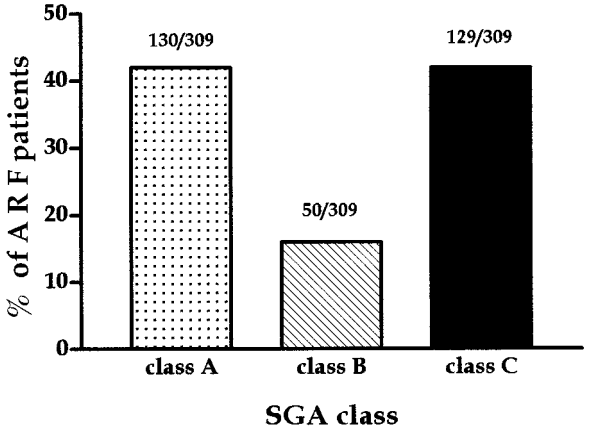

Figure 1. Nutritional status of acute renal failure (ARF) patients on admission. [▨], normal nutritional status; ▧, moderate malnutrition or risk of malnutrition; ■, severe malnutrition.

epidemiologic and clinical aspects of malnutrition in a group of ARF patients using simple, noninvasive, inexpensive bedside methods for the diagnosis of malnutrition; (*2*) determine whether the presence of malnutrition in ARF patients at admission to a renal intermediate care unit, independently of non-nutritional factors, correlates with a poorer outcome, defined as increased incidence of mortality, complications, and use of health care resources.

Materials and Methods

Study Population

All patients consecutively admitted in a 42-mo period (January 1, 1994, to June 30, 1997) for ARF to the renal intermediate care unit of the Internal Medicine & Nephrology Department of a 1500-bed acute care teaching hospital were included in the study. ARF was defined as an abrupt decline in renal function (27) with a recent rise (24 to 48 h) in the plasma creatinine values of more than 50% above the baseline status in the absence of volume responsive prerenal status (28); in the case of preexisting renal disease or known renal insufficiency that had not been dialyzed before, and was not considered end-stage renal disease (ESRD), patients were required to demonstrate an increase in serum creatinine levels >1 mg/dl from their baseline status (acute-on-chronic renal failure) (29). Each patient and/or relatives received a detailed oral explanation as to the nature and purpose of the study, and informed consent was obtained; approval from the local Ethics Committee was not required for the use of data that had already been collected for clinical use. The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki.

In this noninterventional study, the therapy and management of each patient, in particular regarding renal replacement therapies, were determined by the patient's primary physicians, without direct intervention from the investigators. Because medical care in Italy is covered by the National Health System, there was no access restriction to treatment. The standard hemodialysis schedule was at least 4 h every other day; conventional bicarbonate hemodialysis was performed through central venous access by double or triple lumen catheters (internal jugular or subclavian veins) (30), with an ultrafiltration-controlled delivery system, polymethylmetacrylate or polysul-

Table 2. Demographic and clinical characteristics of ARF patients stratified by nutritional status[a]

Characteristic	SGA Class A ($n = 130$)	SGA Class B ($n = 50$)	SGA Class C ($n = 129$)	Statistics
Age (yr)	64 ± 16 (range, 18 to 93)	68 ± 13 (range, 21 to 91)	70 ± 15[b] (range, 22 to 90)	ANOVA $P < 0.05$ Trend $P < 0.01$
Gender	83 M (64%) 47 F (36%)	33 M (66%) 17 F (34%)	81 M (63%) 48 F (37%)	χ^2 for independence NS χ^2 for trend NS
Location				
emergency room	20 (16%)	2 (4%)	9 (7%)	
medical ward	68 (52%)	29 (58%)	80 (62%)	
coronary care unit	3 (2%)	1 (2%)	4 (2%)	
surgical ward	20 (16%)	8 (16%)	18 (14%)	χ^2 for independence NS
surgical ICU	8 (6%)	5 (10%)	6 (5%)	χ^2 for trend NS
trauma ICU	4 (3%)	3 (6%)	6 (5%)	
heart surgery ICU	7 (5%)	2 (4%)	6 (5%)	
Medical ARF	94 (72%)	35 (79%)	98 (76%)	χ^2 for independence NS χ^2 for trend NS
Surgical ARF	36 (28%)	15 (30%)	31 (24%)	χ^2 for independence NS χ^2 for trend NS
Creatinine (mg/dl)	6.7 ± 4.2 (2.0 to 23)	6.2 ± 4.2 (2.0 to 23.1)	5.1 ± 2.7[c] (2.0 to 15.9)	Kruskal–Wallis $P < 0.05$
BUN (mg/dl)	87 ± 49 (27 to 322)	89 ± 48 (27 to 327)	100 ± 48 (34 to 258)	ANOVA NS
Oliguria	68 (52%)	33 (66%)	103 (80%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Renal replacement therapy (hemodialysis or CRRT)	74 (57%)	34 (68%)	99 (77%)[d]	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.001$
Time delay <24 h between admission and RRT start (% of pts on RRT)	70/73 (96%)	31/34 (91%)	97/99 (98%)	χ^2 for independence NS χ^2 for trend NS
No. of patients on hemodialysis	65 (50%)	29 (58%)	79 (61%)	χ^2 for independence NS χ^2 for trend NS
No. of hemodialysis sessions (per patient)	6.2 ± 6.6 (1 to 38) Median 4	7.1 ± 6.3 (1 to 25) Median 5	7.4 ± 9.7 (1 to 48) Median 4	Kruskal–Wallis NS
No. of patients on CRRT	9 (7%)	5 (10%)	20 (16%)[e]	χ^2 for independence NS χ^2 for trend $P < 0.05$
APACHE II	20.2 ± 7.7	23.9 ± 8.1[b]	25.9 ± 7.8[b]	ANOVA $P < 0.001$ Trend $P < 0.001$

[a] SGA, Subjective Global Assessment of nutritional status method; RRT, renal replacement therapy. Other abbreviations as in Table 1.
[b] $P < 0.01$ *versus* SGA class A, Dunnett multiple comparison test.
[c] $P < 0.01$ *versus* SGA class A, Dunn multiple comparison test.
[d] $P < 0.001$ *versus* SGA class A, Fisher exact test.
[e] $P < 0.05$ *versus* SGA class A, Fisher exact test.

Table 3. Acute comorbidities of the ARF patients stratified by nutritional status[a]

Clinical Condition	SGA Class A ($n = 130$)	SGA Class B ($n = 50$)	SGA Class C ($n = 129$)	Statistics
Heart failure	31 (24%)	13 (26%)	51 (40%)[b]	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.01$
DIC	7 (5%)	7 (14%)	18 (14%)[c]	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.05$
GI bleeding	7 (5%)	4 (8%)	14 (11%)	χ^2 for independence NS χ^2 for trend NS
Hepatic failure	7 (5%)	5 (10%)	26 (20%)[d]	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.001$
Hypotension	22 (17%)	10 (20%)	53 (41%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Neurologic failure	12 (9%)	5 (10%)	36 (28%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Oliguria	68 (42%)	33 (66%)	103 (80%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Respiratory failure	42 (32%)	25 (50%)[c]	76 (59%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Sepsis	21 (16%)	13 (26%)	38 (29%)[c]	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.05$
SIRS	53 (41%)	28 (56%)	90 (70%)[d]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$

[a] DIC, disseminated intravascular coagulation; GI, gastrointestinal; SIRS, soluble immune response suppressor. Other abbreviations as in Tables 1 and 2.
[b] $P < 0.01$ *versus* SGA class A, Fisher exact test.
[c] $P < 0.05$ *versus* SGA class A, Fisher exact test.
[d] $P < 0.001$ *versus* SGA class A, Fisher exact test.

fone hollow fiber filters, and heparin as anticoagulant. The heparin-free hemodialysis method with ethylvinylalcohol, polysulfone or polymethylmetacrylate filters was used for patients at hemorrhagic risk. Continuous renal replacement therapy (CRRT) was performed as continuous venovenous hemofiltration by using the same filters as for hemodialysis, with prostacyclin as circuit antiaggregant.

Measurements

Nutritional Status. Nutritional status was evaluated at admission by the Subjective Global Assessment of nutritional status method (SGA) applied by one of two trained clinical examiners. SGA is a clinical technique that assesses nutritional status and malnutrition based on features of the history (weight change, dietary intake, gastrointestinal symptoms that have persisted for >2 wk, functional capacity, underlying disease, and effect of metabolic stress) and physical examination (loss of subcutaneous fat, muscle wasting, ankle edema, sacral edema, and ascites) (31,32). Patients are rated as being subdivided into three classes: well nourished (SGA class A), moderately malnourished or at risk of malnutrition (SGA class B), and severely malnourished (SGA class C). Nutritional status was also evaluated by traditional methods: anthropometric, biochemical, and immunologic parameters, as described previously in detail (33).

Outcome Measures. Variables of potential prognostic significance (demographic data, premorbid conditions, primary and concomitant diagnoses, clinical and laboratory data) were chosen on the basis of both a review of the literature (34–44) and the authors' judgment on the basis of both their clinical or biologic plausibility and epidemiologic importance. Definitions of premorbid conditions, acute comorbidities and complications were derived from the literature (45–49) and are reported in the Appendix. Patients were followed clinically until discharge or death; during the patient's entire hospital stay after ARF diagnosis, each subject was monitored on a daily basis for the development of complications, by chart reviews, interviews with the ward team, and patient examination to confirm data from charts. All complications requiring therapeutic intervention were recorded, as well as final outcome (death or discharge). Clinical outcome was evaluated by the following end points: in-hospital mortality (death during hospital stay), in-hospital morbidity (complications during hospital stay), and use of health care resources (length-of-hospital stay and dialysis dependence at 30 d after discharge). Renal replacement therapies required until death or hospital dismissal or treatment discontinuation were recorded as the total number of dialysis sessions per patient or CRRT hours per patient; no index of the intensity of dialysis delivered was routinely measured during the study. Data were recorded at admission and updated daily, 7 days a week, on preprinted forms by experienced medical personnel involved in the study. Access '97 database (Microsoft) was used for final data recording and processing. To confirm the reliability of the data, 20% of the patient charts were evaluated by the kappa statistic; good agreement (kappa statistic range, 0.80 to 0.90) between the reference group and the audited sample was obtained.

Statistical Analyses

One-way ANOVA with Dunnett post test or Kruskall–Wallis ANOVA with Dunn multiple comparison test were used for comparison of continuous variables depending on distribution of variables.

Discrete data were analyzed by Fisher exact test and the χ^2 test for trend. Independent binary variables found to be significant at univariate analysis were used in a multiple logistic regression procedure, performed by the forward stepwise selection method (entry and exit criteria at the $P = 0.05$ level). The calculation of odds ratio (OR) and its 95% confidence limits (CI) was used for the evaluation of the outcome predictors. Because logistic regression assumes independence of observation, we considered only the first admission for each patient for the entire study. All statistical tests were two-tailed, and significance was accepted at the $P < 0.05$ level. Values are expressed as mean ± SD and range. Statistical analysis was performed on a desktop computer using the Statistical Package for the Social Sciences, version 7.0 (SPSS, Inc., Chicago, IL), and by Prism, version 2.01 (GraphPad Software, San Diego, CA).

Results

Demographic and clinical characteristics of the ARF patient cohort are described in Table 1; most of the patients (278 of 309, 90%) were already hospitalized at the referral for ARF. Nutritional status at admission to the renal intermediate care unit was characterized by a high prevalence of severe malnutrition, which was individuated in 129 of 309 patients (42%) according to their status as SGA class C; 130 of 309 subjects (42%) had normal nutritional status (Figure 1). Table 2 shows demographic and clinical characteristics of ARF patients stratified by nutritional status. Compared to subjects with normal nutritional status, patients with severe malnutrition were older and had lower serum creatinine levels, they were more frequently oliguric, and renal replacement therapies, in particular CRRT, were performed more often. No difference was found in the number of hemodialysis sessions per patient between the three subgroups of ARF patients; APACHE II score of severely malnourished patients had the highest value. A statistically significant trend toward increasing acute and chronic comorbidity prevalence, ranging from normal nutritional status to moderate and severe malnutrition, was evident; SGA class C patients had the highest incidence of heart failure, disseminated intravascular coagulation, hepatic failure, hypotension, neurologic failure, respiratory failure, sepsis, and septic shock (Table 3). The same subgroup of ARF patients was characterized by a statistically significant increase in the frequency of chronic hepatic disease, chronic obstructive pulmonary disease, and immunodepression (Table 4). Univariate analysis of traditional nutritional indexes confirmed that SGA class C status was associated with the lowest anthropometric, biochemical, and immunologic parameters (Table 5). In most of the patients (214 of 309, 69.2%), artificial nutrition was started after referral for ARF: 113 of 129 (87.6%) of class C patients (84 on parenteral, 29 on enteral nutrition), 38 of 50 (76%) of class B patients (31 on parenteral, seven on enteral nutrition, and 63 of 130 (48.5%) of class A patients (50 on parenteral, 13 on enteral). Severe malnutrition, as compared to normal nutritional status, was associated with a statistically significant increase of death risk (Figure 2) and morbidity: Infectious complications, hemorrhagic risk and gastrointestinal bleeding, cardiac dysrhythmia, cardiogenic shock, and mechanical ventilation need were more frequently present in severely malnourished patients (Table 6). In the latter subgroup of ARF patients, the use of health resources was significantly increased as well (Table 7). No formal assessment of quality of life was obtained in survivors after discharge. Preexisting malnutrition was a statistically significant, independent predictor of in-hospital mortality at

Table 4. Chronic comorbidities of the ARF patients stratified by nutritional status[a]

Comorbidity	SGA Class A ($n = 130$)	SGA Class B ($n = 50$)	SGA Class C ($n = 129$)	Statistics
Active malignancy	25 (19%)	14 (28%)	36 (28%)	χ^2 for independence NS χ^2 for trend NS
Atherosclerotic vascular disease	35 (27%)	18 (36%)	29 (22%)	χ^2 for independence NS χ^2 for trend NS
Chronic hepatic disease	21 (16%)	13 (26%)	43 (33%)[b]	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.01$
COPD	25 (19%)	15 (30%)	42 (32%)[c]	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.05$
Diabetes mellitus	13 (10%)	7 (14%)	17 (13%)	χ^2 for independence NS χ^2 for trend NS
Heart disease	64 (49%)	20 (40%)	66 (51%)	χ^2 for independence NS χ^2 for trend NS
valvular	8 (6%)	3 (6%)	12 (9%)	
ischemic	32 (25%)	14 (28%)	37 (29%)	
other	24 (18%)	3 (6%)	17 (13%)	
Immunodepression	15 (11%)	11 (22%)	29 (22%)[c]	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.05$

[a] COPD, chronic obstructive pulmonary disease. Other abbreviations as in Tables 1 and 2.
[b] $P < 0.01$ *versus* SGA class A, Fisher exact test.
[c] $P < 0.05$ *versus* SGA class A, Fisher exact test.

Table 5. Nutritional indexes (anthropometric, biochemical, and immunologic) of the ARF patients stratified by nutritional status[a]

Parameter	SGA Class A (n = 130)	SGA Class B (n = 50)	SGA Class C (n = 129)	Statistics
TSF (mm)	14.4 ± 5.3 (range, 2 to 29) (n = 113)	11.4 ± 3.8[b] (range, 3 to 19) (n = 48)	8.9 ± 4.0[b] (range, 1.5 to 18) (n = 116)	Kruskall–Wallis $P < 0.001$
% of patients with TSF <5°	10 of 112 (9%)	8 of 48 (17%)	54 of 117 (46%)[c]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
AMA (cm^2)	5021 ± 1196 (n = 111) (range, 2158 to 8433)	4407 ± 946[d] (n = 47) (range, 2885 to 6723)	3676 ± 871[b] (n = 115) (range, 1564 to 6860)	Kruskall–Wallis $P<0.001$
% of patients with AMA <5°	16 of 112 (14%)	11 of 48 (23%)	62 of 117 (53%)[c]	χ^2 for independence $P < 0.001$ χ^2 for trend $P < 0.001$
Albumin (g/dl)	3.1 ± 0.5 (n = 128) (range, 2 to 4.6)	3.0 ± 0.6 (n = 50) (range, 1.8 to 4.4)	2.7 ± 0.7[e] (n = 128) (range, 1.4 to 4.4)	ANOVA $P<0.001$
Transferrin (mg/dl)	131 ± 43 (n = 109) (range, 30 to 306)	128 ± 56 (n = 46) (range, 16 to 326)	98 ± 47[b] (n = 104) (range, 3 to 298)	Kruskall–Wallis $P<0.001$
Prealbumin (mg/dl)	21.1 ± 9.4 (n = 107) (range, 5 to 45.6)	17.2 ± 8.3[f] (n = 45) (range, 2.5 to 37.6)	15.3 ± 9.1[e] (n = 102) (range, 2.5 to 42.6)	ANOVA $P<0.001$ Trend $P < 0.001$
Total lymphocyte count (mm^3)	1148 ± 586 (n = 111) (320 to 3550)	1101 ± 542 (n = 44) (range, 300 to 2460)	904 ± 432[g] (n = 103) (range, 120 to 2190)	Kruskall–Wallis $P<0.01$
IgG (mg/dl)	1340 ± 612 (n = 110) (range, 303 to 3920)	1247 ± 478 (n = 45) (range, 378 to 2722)	1296 ± 608 (n = 100) (range, 124 to 2806)	Kruskall–Wallis NS
IgA (mg/dl)	309 ± 147 (n = 110) (range, 35 to 714)	315 ± 158 (n = 45) (range, 89 to 640)	329 ± 195 (n = 100) (range, 18 to 886)	Kruskall–Wallis NS
IgM (mg/dl)	153 ± 126 (n = 110) (range, 21 to 892)	170 ± 148 (n = 45) (range, 28 to 923)	126 ± 81 (n = 100) (range, 15 to 757)	Kruskall–Wallis NS

[a] TSF, triceps skinfold; AMA, arm muscle area. Other abbreviations as in Tables 1 and 2.
[b] $P < 0.001$ *versus* SGA class A, Dunn multiple comparison test.
[c] $P < 0.001$ *versus* SGA class A, Fisher exact test.
[d] $P < 0.05$ *versus* SGA class A, Dunn multiple comparison test.
[e] $P < 0.01$ *versus* SGA class A, Dunnett multiple comparison test.
[f] $P < 0.05$ *versus* SGA class A, Dunnett multiple comparison test.
[g] $P < 0.01$ *versus* SGA class A, Fisher exact test.

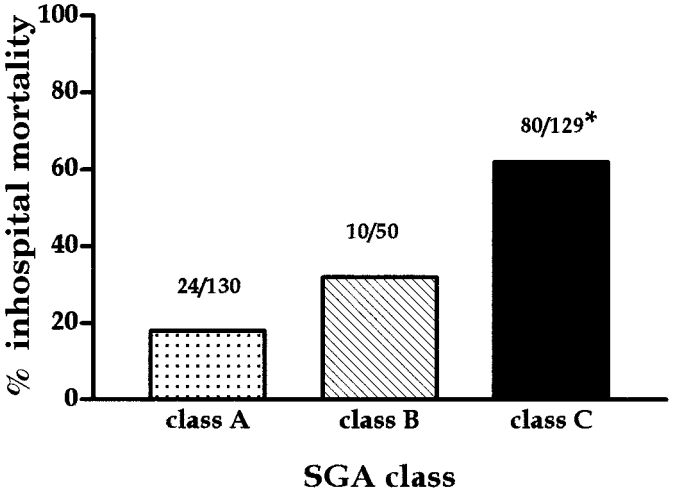

Figure 2. In-hospital mortality according to nutritional status. ▨, normal nutritional status; ▧, moderate malnutrition or risk of malnutrition; ■, severe malnutrition. χ^2 for trend ($P < 0.001$). *$P < 0.001$ *versus* class A, Fisher exact test (Odds ratio 7.21; 95% confidence interval, 4.08 to 12.73).

multivariable logistic regression analysis both with comorbidities (OR 2.02; 95% CI, 1.50 to 2.71, $P < 0.001$) (Table 8), and with comorbidities and complications (OR 2.12; 95% CI, 1.61 to 2.89, $P < 0.001$) (Table 9). The increased risk of mortality associated with severe malnutrition was also evident when ARF patients were stratified by both severity of illness and nutritional status. In patient subgroups with similar APACHE II scores, mortality rates at each stratum of severity of illness were higher in subjects with severe malnutrition (Table 10).

Discussion

Our study demonstrates that malnutrition is highly prevalent in ARF patients at the time of referral to a specialized nephrology unit, and that in this clinical condition patient outcome is significantly and negatively affected by a poor nutritional status, independently from non-nutritional factors (acute and chronic comorbidities). The high prevalence of malnutrition in the patients considered in the present study is not surprising, given the fact that 90% of patients were already hospitalized, the high number of acute and chronic comorbidities, and the well known negative impact of hospitalization on nutritional status (9–21). As for patient risk stratification, *i.e.*, the prevalence of acute and chronic comorbidities at admission, our cohort can be considered fairly representative of ARF patient populations commonly hospitalized in nephrology wards or intermediate care units. This, along with the prospective design of the study, allowed a correct definition of the respective prognostic role of nutritional status alterations and of non-nutritional factors in ARF.

Many problems arise from the analysis of literature on factors influencing ARF outcome. In fact, available data are in most cases retrospective, are derived mainly from surgical or intensive care unit patient populations, and deal almost exclusively with dialysis-requiring ARF (3,5,6,37–39,42,50–58). A key problem with this type of study is that little or no mention is usually made of nutritional status, possibly because of the well known difficulty of nutritional status evaluation in critically ill patients. At present there is no gold standard yet for the diagnosis of malnutrition in hospitalized patients (59,60). Diagnostic accuracy of traditional methods (anthropometric, biochemical, or immunologic) is in fact negatively affected by several non-nutritional factors (61–63), especially in patients with renal disease (64,65). SGA is a simple, multifactorial assessment method for nutritional status evaluation; is based on the clinician's experience; and is composed of a carefully performed dietary and medical history, physical examination, and functional assessment (31–32). SGA has been demonstrated to be a valuable and inexpensive tool in the nutritional assessment of surgical patients (66,67), liver (68) and lung transplant candidates (69), and end-stage renal disease patients (70–73). Interobserver reproducibility is good in patients with either chronic (70) or acute renal failure (74).

In our study, the SGA method was validated in two ways. By parallel quantitative evaluation of traditional nutritional parameters, a consistent worsening of several traditional objective nutritional indexes was demonstrated, with the worst values found in the group of severely malnourished patients. Moreover, by the analysis of the impact of nutritional status classification by SGA on patient outcome, a statistically significant trend to increasing in-hospital mortality from SGA class A to class C was demonstrated. SGA class C patients also had the highest prevalence of complications, in particular sepsis and septic shock. Many potential mechanisms and causes contribute to the increased susceptibility to infection that characterizes the uremic state (5,44,75–81). Nutritional factors could also play an important role, malnutrition being *per se* associated with altered immune response and increased infection risk (82).

Several important limitations of this study should be mentioned. First, as previously discussed, even though SGA has been used in several different clinical settings (66–73), it should be emphasized that the method has been mainly derived in surgical patients. Second, despite our large sample size and the relatively limited number of variables considered, there are well known limits of logistic regression analysis when developing multivariable models (83). In our case, too, the validity of the derived prediction model is to be verified in other populations, possibly from other institutions. Third, although our study suggests that poor nutritional status negatively affects ARF patient outcome independently from non-nutritional factors, only by nutritional intervention studies would it be possible to prove causality, *i.e.*, to determine whether an improvement in nutritional status is associated with a reduction in death rate, complications, and use of health care resources. In fact, randomized controlled trials involving parenteral administration of formulas enriched with essential amino acids showed no definite improvement in mortality rates (22–26). As a matter of fact, relevant differences in quantitative and qualitative aspects of nutritional support, patient selection, as well as limits in study design, make the interpretation of these conflicting results difficult (84). Fourth, aside from the pres-

Table 6. Clinical outcome of ARF patients stratified by nutritional status: complications during hospital stay[a]

Complication	SGA Class A ($n = 130$)	SGA Class B ($n = 50$)	SGA Class C ($n = 129$)	Statistics
Sepsis	17 (13%)	15 (30%)[b] OR 2.85 (1.53 to 5.42)	39 (29%)[c] OR 2.88 (1.53 to 5.42)	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.001$
Septic shock	5 (4%)	3 (6%)	18 (14%)[d] OR 4.05 (1.46 to 11.28)	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.01$
Surgical wound infection	4 (3%)	4 (8%)	11 (9%)	χ^2 for independence NS χ^2 for trend NS
Hemorrhage	12 (9%)	12 (24%)[b] OR 3.1 (1.29 to 7.49)	30 (23%)[d] OR 2.98 (1.45 to 6.13)	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.01$
GI bleeding	11 (8%)	7 (14%)	22 (17%)[b] OR 2.22 (1.03 to 4.80)	χ^2 for independence NS χ^2 for trend $P < 0.05$
Intestinal occlusion	3 of 130 (2%)	3 of 50 (3%)	15 of 129 (12%)[d] OR 5.57 (1.57 to 19.74)	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.01$
Cardiogenic shock	7 (5%)	7 (14%)	26 (20%)[c] OR 4.39 (1.83 to 10.55)	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.01$
Cardiac dysrhythmias	35 (27%)	16 (32%)	59 (46%)[d] OR 2.29 (1.36 to 3.85)	χ^2 for independence $P < 0.01$ χ^2 for trend $P < 0.01$
Acute respiratory failure requiring mechanical ventilation	6 (5%)	2 (4%)	18 (14%)[b] OR 3.35 (1.28 to 8.74)	χ^2 for independence $P < 0.05$ χ^2 for trend $P < 0.01$

[a] OR, odds ratio *versus* class A, with 95% confidence interval in parentheses. Other abbreviations as in Tables 1, 2, and 3.
[b] $P < 0.05$ *versus* SGA class A, Fisher exact test.
[c] $P < 0.001$ *versus* SGA class A, Fisher exact test.
[d] $P < 0.01$ *versus* SGA class A, Fisher exact test.

Table 7. Clinical outcome of ARF patients stratified by nutritional status: use of health care resources[a]

	SGA Class A ($n = 130$)	SGA Class B ($n = 50$)	SGA Class C ($n = 129$)	Statistics
Dialysis dependence (survivors, at 30 days from discharge)	28 of 106 (26%)	7 of 34 (21%)	19 of 59 (32%)	χ^2 for independence NS χ^2 for trend NS
Hospital LOS, days	23.5 ± 14.6	35.1 ± 29.9[b]	34.8 ± 27.7[c]	ANOVA $P < 0.01$
(survivors)	($n = 106$)	($n = 34$)	($n = 59$)	
	(range, 1 to 70)	(range, 8 to 120)	(range, 1 to 104)	
total	26 ± 20	28 ± 27	28 ± 26	ANOVA NS
	($n = 130$)	($n = 50$)	($n = 129$)	

[a] LOS, length of hospital stay. Other abbreviations as in Tables 1 and 2.
[b] $P < 0.05$ *versus* SGA class A, Dunnett multiple comparison test.
[c] $P < 0.01$ *versus* SGA class A, Dunnett multiple comparison test.

ence of malnutrition at admission, the outcome of the patients we studied may have been affected by other important nutritional factors. In particular, the extent of catabolism and consequent nitrogen depletion and calorie deficit, as well as nutritional management during hospital stay (84,85). It is well known that nutritional status declines after hospitalization for acute illness (11,13–15). Lack of attention to the actual nutrient intake and inadequate utilization of artificial nutrition support do represent major factors (13–15,86,87). In ARF patients hypercatabolism could also play an important role (84,85,88–90). Because the main purpose of our study was to define the prognostic impact of malnutrition as a comorbidity (*i.e.*, at the time of ARF diagnosis), and not as a complication of ARF clinical course, no nutritional survey was performed in our patients during hospital stay, and quantitative and qualitative aspects of nutritional support were not investigated. Nevertheless, preliminary results from our institution suggest that a lack of adequacy of artificial nutrition in ARF patients is not uncommon, and in fact is even more evident in the case of patients on parenteral compared with enteral nutrition (91). Finally, it is also well known that in ESRD patients, morbidity and mortality are inversely related to the delivered dialysis dose (19,20), and recent data suggest that also in ARF patients, renal replacement therapy (RRT) delivery (in particular the

Table 8. Multivariable analysis of in-hospital mortality predictors in ARF patients: comorbidities (acute and chronic)[a]

Variable	OR	95% CI	*P* Value
Age	1.05	1.02 to 1.07	<0.001
GI bleeding	5.82	2.02 to 16.76	<0.001
Heart failure	2.02	1.04 to 3.95	<0.05
Hepatic failure	2.75	1.27 to 5.99	<0.05
Hypotension	2.05	1.03 to 4.06	<0.05
Immunodepression	3.09	1.37 to 7.02	<0.01
Respiratory failure	3.14	1.82 to 5.42	<0.001
SGA class C	2.02	1.50 to 2.71	<0.001

[a] Abbreviations as in Tables 1, 2, and 6.

Table 9. Multivariable analysis of in-hospital mortality predictors in ARF patients: comorbidities (acute and chronic) and complications[a]

Variable	OR	95% CI	*P* Value
Age[b]	1.04	1.02 to 1.06	<0.01
Cardiogenic shock[c]	26.73	10.12 to 70.59	<0.001
GI bleeding[b]	3.43	1.23 to 9.54	<0.05
GI bleeding[c]	3.25	1.44 to 7.33	<0.05
Respiratory failure[b]	2.09	1.15 to 3.80	<0.05
Septic shock[c]	29.41	7.37 to 117.41	<0.001
SIRS[c]	2.43	1.27 to 4.64	<0.05
SGA class C	2.16	1.61 to 2.89	<0.001

[a] Abbreviations as in Tables 1, 2, 3, and 6.
[b] Comorbidities.
[c] Complications.

way and the amount of RRT) may have some impact on survival (92–95). In our study, we did not formally assess the dose and the adequacy of RRT, so we cannot exclude that differences in the RRT dose, allowing more adequate nutritional support, could have resulted in different outcomes, *i.e.*, in malnourished and/or more catabolic ARF patients.

As recently stressed for ESRD patients on chronic hemodialysis, the debate is still ongoing as to whether malnutrition is a marker of illness, *i.e.*, a simple mirror of the multiple acute and chronic comorbidity effects, or a real independent risk factor, *i.e.*, a direct cause of death that may aggravate existing comorbidities (64,65). In our study, inclusion in SGA class C represented a statistically significant risk factor for death, independently from the severity of the underlying illnesses. Mortality was in fact higher in patients with severe malnutrition than in patients with a similar APACHE II score (and probably a comparable severity of illness), but without nutritional status alterations. Again, while in the case of ESRD patients there is some evidence that the treatment of malnutrition is *per se* able to improve the risk of death, up to now no study has clearly ascertained to what extent inadequate nutritional intake accounts for the relationship between malnutrition and mortality in ARF patients. However, it is evident that a definitive answer to that question can only come from nutritional intervention controlled studies in patients with comparable severity of illness.

Despite its limitations, the present study has demonstrated for the first time in the literature that nutritional status alterations, as assessed by the SGA method at admission to nephrology wards, are a frequent finding in hospitalized patients with ARF, and that in these patients severe, preexisting malnutrition is associated with a negative hospital outcome. The main clinical utility of the SGA method in the case of ARF patients is for risk stratification, because the method allows easy identification of high-risk subgroups of ARF patients who probably need aggressive nutritional intervention. Because these are the patients most at risk for malnutrition-associated morbidity and mortality, evaluation of nutritional status in ARF patients should become a part of both routine clinical assessment and prognostic stratification before interventive studies.

Appendix: Definitions

Acute Morbidities

Heart failure: Class IV New York Heart Association, or low cardiac output (cardiac index <2.5 L/min per m^2, or left ventricular ejection fraction <30%), or requiring inotropic support (dopamine >4 μg/kg per min and/or dobutamine whatever dose).

Catabolism: Blood urea nitrogen increase >30 mg/dl per d or total nitrogen appearance >10 g/d, in the 24 h immediately before or after admission.

Disseminated intravascular coagulation: Platelet count $<100 \times 109$/L and prothrombin time >16 s with positive test for fibrin split products or ≥2 U of fresh frozen plasma infused in the past 24 h.

Gastrointestinal bleeding: Hematemesis or melena in the past 48 h, with or without need for blood transfusion.

Hepatic failure: Total bilirubin >4.0 mg/dl with prothrombin time >16 s or alanine-aminotransferase >100 U/L, or hepatic encephalopathy.

Hypotension: Systolic BP ≤90 mmHg for 2 h in the 24 h after admission.

Neurologic failure: Coma or deep stupor (Glasgow scale ≤6 without sedation).

Oliguria: Urinary output <500 ml/24 h or <20 ml/h in the past 8 h.

Respiratory failure: Arterial oxygen saturation <90% or PaO_2 <60 mmHg, and/or $PaCO_2$ >50 mmHg.

Sepsis: The systemic response to infection, manifested by two or more of the following conditions as a result of infection: Temperature >38°, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, WBC >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms.

Septic shock: Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

SIRS: The systemic inflammatory response to a variety of

Table 10. Mortality of ARF patients stratified by both severity of illness (APACHE II score) and nutritional status (SGA)[a]

APACHE II Score	No. of Patients	SGA Class	In-Hospital Mortality	Statistics
5 to 15	57	A ($n = 37$)	3 of 37 (9%)	
		B ($n = 11$)	3 of 11 (27%)	χ^2 for trend $P < 0.05$
		C ($n = 8$)	3 of 8 (38%)[b]	
16 to 25	146	A ($n = 70$)	10 of 70 (14%)	
		B ($n = 21$)	3 of 21 (14%)	χ^2 for trend $P < 0.001$
		C ($n = 55$)	27 of 55 (49%)[c]	
26 to 35	87	A ($n = 18$)	6 of 18 (33%)	
		B ($n = 13$)	6 of 13 (46%)[b]	χ^2 for trend $P < 0.01$
		C ($n = 56$)	42 of 56 (75%)[c]	
>35	19	A ($n = 5$)	5 of 5 (100%)	
		B ($n = 5$)	4 of 5 (80%)	χ^2 for trend NS
		C ($n = 9$)	8 of 9 (89%)	

[a] Abbreviations as in Tables 1 and 2.
[b] $P < 0.05$ *versus* SGA class A, Fisher exact test.
[c] $P < 0.001$ *versus* SGA class A, Fisher exact test.

severe clinical insults. The response is manifested by two or more of the following conditions: Temperature >38°, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, WBC >12,000 cells/mm^3 or <4000 cells/mm^3, or >10% immature (band) forms.

Chronic Comorbidities

Active malignancy: Non-skin cancer.

Atherosclerotic vascular disease: Angina or myocardial infarction or claudication or history of vascular bypass surgery.

Chronic renal insufficiency: Serum creatinine ≥3.0 mg/dl before the ARF episode.

Chronic obstructive pulmonary disease: History, physical exam, and x-rays, compatible with chronic obstructive pulmonary disease, resulting in functional disability and/or requiring chronic bronchodilator therapy and/or FEV1 <75% predicted.

Chronic hepatic disease: History of heavy alcohol use with portal hypertension and varices, other causes with evidence of portal hypertension and varices, or biopsy confirmation, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, prior episodes of encephalopathy/hepatic coma.

Diabetes mellitus: Treatment before hospitalization.

Heart disease: Ischemic or valvular heart disease, or other (hypertensive, dilatative cardiomyopathy, chronic cor pulmonale, etc).

Immunodepression: Therapy that suppresses resistance to infection, *e.g.*, immunosuppression, chemotherapy, radiation, long-term or recent high-dose steroids, or diseases that are sufficiently advanced to suppress resistance to infection (leukemia, lymphoma, AIDS, etc.)

Complications

Cardiac dysrhythmia: Cardiac arrhythmia, paroxysmal tachycardia, fibrillation with rapid ventricular response, second- or third-degree heart block; does not include chronic and stable arrhythmias.

Cardiogenic shock: Mean arterial BP ≤49 mmHg or systolic arterial blood pressure <60 mmHg.

Gastrointestinal bleeding: See acute comorbidities.

Intestinal occlusion: Mechanic or paralytic ileus.

Respiratory failure: New episode after ARF diagnosis requiring mechanical ventilation (including controlled mechanical ventilation, continuous positive airway pressure and noninvasive pressure support ventilation).

Sepsis and septic shock: See acute comorbidities.

Surgical wound infection: Sepsis and/or septic shock and infection of a recent (≤10 d) surgical wound with need for surgical revision.

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