Is Malnutrition Overdiagnosed in Older Hospitalized Patients? Association Between the Soluble Interleukin-2 Receptor and Serum Markers of Malnutrition

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Background. Many researchers have speculated that markers of malnutrition such as albumin, prealbumin, cholesterol, and transferrin are influenced by inflammation. The mechanism of this interaction has not been well understood.

Methods. This was a prospective cross-sectional study. We evaluated 72 male patients older than 60 years admitted to a geriatric rehabilitation unit. Subjects with severe hepatic or renal diseases were excluded. We measured body mass index, caloric intake, serum albumin, prealbumin, cholesterol, transferrin, hemoglobin, and total lymphocyte count. To detect inflammation, we measured C-reactive protein, Westergren sedimentation rate, fibrinogen, and cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-2, and the soluble IL-2 receptor.

Results. Soluble IL-2 receptor was negatively associated with albumin ($r = -.479$, $p < .0001$), prealbumin ($r = -.520$, $p =< .0001$), cholesterol ($r = -.487$, $p = .0001$), transferrin ($r = -.455$, $p = .0002$), and hemoglobin ($r = -.371$, $p = .002$). TNF-α, IL-1β, IL-6, and IL-2 were not associated with these measures.

Conclusions. Inflammation increases the incidence of hypoalbuminemia and hypocholesterolemia, potentially leading to overdiagnosis of malnutrition. We suggest that albumin, cholesterol, prealbumin, and transferrin be used with caution when assessing the nutritional status of older hospitalized patients. In the future, soluble IL-2 receptor levels might be used to correct for the impact of inflammation on these markers of malnutrition.

MALNUTRITION is a common problem in elderly adults and is associated with excess morbidity and mortality (1–3). The diagnosis of malnutrition depends upon history, anthropometric measurements (body mass index, skinfold measurements), dietary measurements (calorie counts), and laboratory data. Serum albumin is the most commonly used laboratory variable, and total lymphocyte count and cholesterol are also commonly used. Less frequently used indicators of protein-energy malnutrition include prealbumin, transferrin, hemoglobin/hematocrit, retinol binding protein, insulin-like growth factor I, and nitrogen balance studies (4–9). Many of these indicators (albumin, prealbumin, and transferrin) are known to be affected by acute illness, but the mechanism has not been understood.

The synthesis of albumin decreases during fasting (10). Serum levels decrease with fasting in hospitalized patients (11) and in animals fed a low protein diet with adequate calories (12). In fasting without concomitant disease, serum albumin levels may be slightly reduced or normal (13,14). In critically ill surgical patients, serum albumin will increase in response to nutritional support in some patients and decrease in others (7). A similar experience has been shown in ventilator patients. With aggressive nutritional support, some patients show an increase in albumin, whereas others show a decline (15).

Albumin levels are also influenced by stress such as surgery, hypothermia (16), and inflammation (17,18). In fact, albumin, prealbumin, and transferrin are negative acute phase reactants (19). The acute phase response is mediated by several cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1β) and IL-6. Other cytokines play a role in the immune response, most notably IL-2, which is necessary for normal T cell function. The IL-2 receptor (IL-2R) is also important for T cell function, and the soluble form (sIL-2Rα, also known as p55, T_{ac}, or CD 25) is readily measured in human serum.

Hypoalbuminemia is common in elderly hospitalized patients and is associated with excess morbidity and mortality (20,21). We and others have shown that hypoalbuminemia occurs frequently in geriatric rehabilitation patients (22). We found that serum albumin predicted institutionalization whereas body mass index (BMI) did not, although both are indicators of nutritional status. To explain this discrepancy, we postulated that inflammation influences serum albumin level in some of these patients. Subsequently, inflammation may affect our nutritional assessment rather than the patient's actual nutritional status. Therefore, we mea-

sured markers of both nutritional status and inflammation (proinflammatory cytokines) to evaluate their relationship.

METHODS

Patients were enrolled from the Geriatric Rehabilitation and Discharge Planning Unit (GRDPU) at the McGuire Veterans Affairs (VA) Medical Center. The GRDPU is an inpatient unit that accepts patients from other wards who require rehabilitation prior to discharge or who have special discharge planning needs. Patients were excluded if they were younger than 60 years old or had severe liver disease (history of ascites) or renal disease (proteinuria >0.30 g/L or >1 g/day or end stage renal disease). Informed consent was obtained from the patient or next of kin if the subject did not have capacity to give consent.

The subject's weight, height, triceps skinfold, and mid-arm circumference were obtained upon admission to the GRDPU. All skinfold measurements were obtained by the same investigator (A.J.R.). Body mass index, midarm muscle area, and percent of the median for triceps skinfold, midarm circumference, and midarm muscle area were calculated by using the Compu-Cal calculator (Compu-Cal, Olympia, WA). Charts were reviewed to determine the primary diagnosis and history of recent infection (within 3 weeks) for each subject.

A dietitian evaluated all subjects upon enrollment using a standard VA scale as described in the appendices. A 3-day calorie count was initiated 1 day after enrollment. Intake was recorded by the dietician, nursing staff, and the investigators.

Upon enrollment, fasting blood was drawn for evaluation of serum albumin, cholesterol, prealbumin, transferrin, hemoglobin, hematocrit, Westergren sedimentation rate (ESR), C-reactive protein (CRP), total lymphocyte count (TLC), and fibrinogen. Serum for cytokine assays was frozen immediately at $-70°C$. Samples were stored in triplicate to avoid excess freeze-thaw cycles.

For all cytokine assays, samples were thawed at room temperature. TNF-α, IL-1β, and IL-6 were assayed using Biokine kits (T Cell Diagnostics, Woburn, MA; sensitivities 10 pg/ml, 4.3 pg/ml, and 45 pg/ml, respectively). IL-2 and sIL-2R (a subunit) were also assayed (Genzyme, Cambridge, MA; sensitivity for both 100 pg/ml). Each assay was run in duplicate or two separate days. All plates were read on the Softmax Molecular Devices (Mountain View, CA) kinetic microplate reader.

Frequencies were analyzed for demographic data. Pearson's correlation and multiple regression analyses were used to test relationships between measures of nutrition and inflammation. Multivariate analysis was used to test the relationship between all cytokines and albumin. Software from SPSS (Chicago, IL) was used to perform the analysis.

RESULTS

Demographics and Clinical Data

One hundred forty-five patients were screened between August 1993 and August 1994. Twelve refused to participate. Consent could not be obtained from another 30 patients. Two were excluded for liver disease and 21 for renal disease. Eight were excluded because they were younger than 60 years old. No women were admitted during the enrollment period. Of the 145 patients screened, 72 men were enrolled. The initial 45 enrolled were consecutive, and the final 27 constituted a convenience sample.

The average age was 73.5 years. The majority of patients (.78) were admitted to the hospital from home. The most common admitting diagnoses were infectious, followed by neurologic and cardiovascular. Nine patients (.13) had a primary diagnosis of cancer. Thirty-nine patients (.54) had an infection within 3 weeks of data collection. Infection was most commonly urinary (.50) or pulmonary (.26). Of the 39 patients with infection, only 14 had fever greater than 100.5°F or white blood counts greater than 10,000/μL. Average length of stay prior to transfer to the GRDPU was 21 days, and mean length of stay on the GRDPU was 40 days (range, 1–129). Twenty-six (.38) were discharged to a nursing home.

Nutritional Status

Many subjects had a history of acute or chronic weight loss. Fifteen patients (.21) lost 5–10% of their usual weight 1 month prior to enrollment, and seven (.10) lost >10% during the same time period. Eighteen patients (.25) lost 10% or more of their usual weight over the 6 months prior to enrollment.

Nutritional status was determined by the dietitian using criteria from Appendix A. Twenty-three (.32) were mildly compromised, 30 (.42) were moderately compromised, and 19 (.26) were severely compromised. Nutritional class was also determined. Nine patients (.13) were diagnosed with severe protein-calorie malnutrition (kwashiorkor, see Appendix B). Nearly half of the patients required some assistance with feeding. Average caloric intake was 1579 kcal/day, and average protein was 64.0 g/day. A summary of anthropometric measurements is shown in Table 1.

Laboratory Analysis

Laboratory results are summarized in Tables 2 and 3. For cytokine assays, standard curve correlation was at least .99 for all assays. Controls included in kits for sIL-2R were within 4% of each other and within the expected range provided by the manufacturer.

Cytokines were correlated with laboratory measures of malnutrition. Regression analysis correcting for age revealed a strong inverse relationship between serum albumin, prealbumin, cholesterol, transferrin, hemoglobin, and sIL-2R (Figure 1). Because the two highest values of sIL-2R must be viewed as outliers, the analysis was repeated after elimi-

Table 1. Anthropometric Measurements
of 72 Elderly Male Veterans

Measurement	Mean	Range	Average Percent of Median
BMI (kg/M^2)	21.8	13.4–32.9	—
Triceps skinfold (mm)	12.3	3–35	59.4
Midarm circumference (cm)	27.7	9–38.5	91.0
Midarm muscle area (cm^2)	48.1	15.7–86	108.7

Table 2. Biochemical Markers of Inflammation
and Nutritional Status

Marker	Mean	Range	Standard Deviation
Albumin (g/L)	34	17–48	6.3
Prealbumin (mg/dL)	22.5	4.7–42.7	8.65
Transferrin (g/L)	2.16	.72–4.09	0.68
Hemoglobin (g/L)	115	77–163	19
TLC (cells/L)	1534	113–5068	850
Cholesterol (mg/dL)	166	70–281	47
ESR (mm/hr)	69	4–150	41
CRP (g/L)	.05	.002–.25	.07

Table 3. Serum Cytokines

	Mean (pg/ml)	Range (pg/ml)	Normal Range (pg/m)	Percent with Detectable Level
TNF-α	1.4	0.0–3.8	0.2–7.1	19
IL-1β	25.2	0.3–120.1	0.1–4.0	100
IL-6	7.0	0.0–43.2[a]	0.4–10.1	58
IL-2	298	0.0–1334[b]	150–4050	71
sIL-2R	2893	680–13,264	500–2250	100

[a]Outlier 1911.
[b]Outlier 2270.

nating these two highest values. The relationships between sIL-2R and nutritional markers remained significant (correlation with albumin, $r = -.397$; prealbumin, $r = -.405$, $p = .0005$; cholesterol, $r = -.305$, $p = .0014$; transferrin, $r = -.314$, $p = .0081$; hemoglobin, $r = -.306$, $p = .0101$).

There was no relationship between nutritional markers and TNF-α, IL-1β, IL-6, and IL-2. On multivariate analysis, only the sIL-2R (of all five cytokines) was related to serum albumin ($p = .046$). No significant relationship was found between any of the cytokines and total lymphocyte count. None of the cytokines were associated with caloric intake or skinfold measurements. BMI correlated with TNF-α ($r = .270$, $p = .022$) but not with the other cytokines. Associations between anthropometric and laboratory data are shown in Table 4.

Soluble IL-2R was compared to other serum markers of inflammation. There was a positive correlation between sIL-2R and CRP ($r = .436$, $p < .0001$) and also fibrinogen ($r = .259$, $p = .028$). There was no significant relationship between ESR and sIL-2R.

DISCUSSION

We found an inverse relationship between sIL-2R and many serum measures of malnutrition, specifically serum albumin, prealbumin, cholesterol, transferrin, and hemoglobin. This study suggests that inflammation affects nutritional assessment and not necessarily nutritional status. If sIL-2R reflects inflammation, a diagnosis of malnutrition that depends on albumin, prealbumin, cholesterol, and/or transferrin should be made with caution.
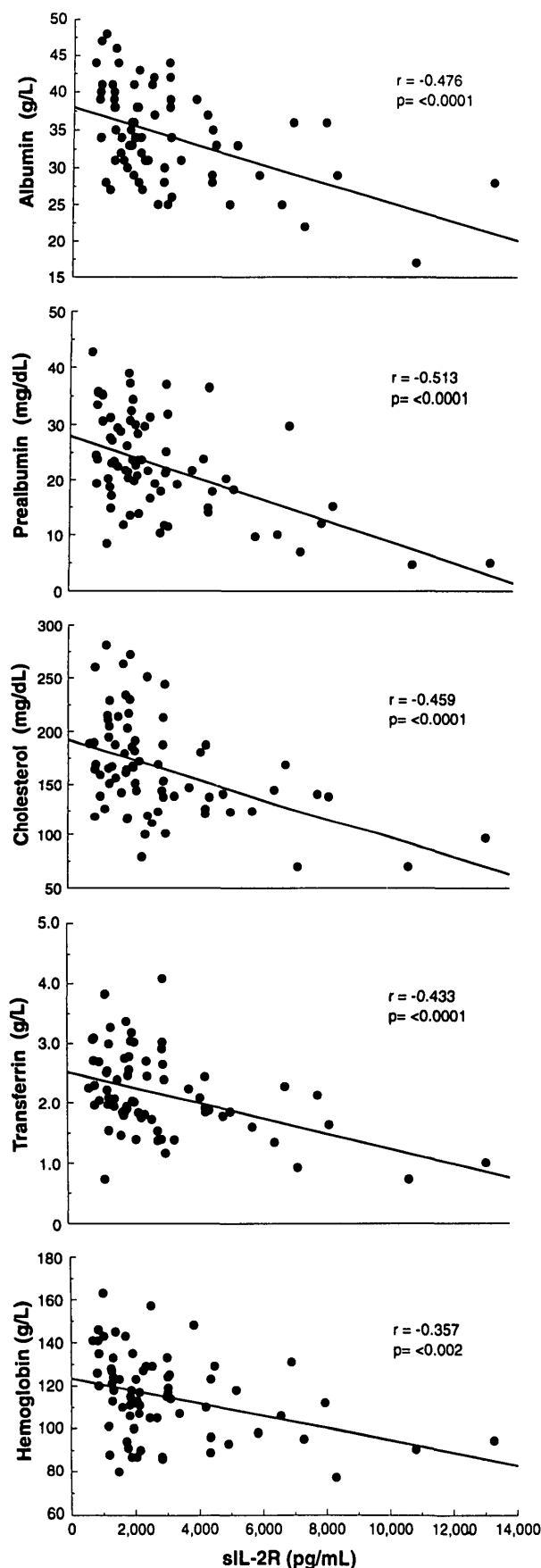

Figure 1. sIL-2R and markers of malnutrition.

Table 4. Associations Between Anthropometric and Serum Measures of Malnutrition

Measure	Albumin	Prealbumin	Cholesterol	Transferrin	Total Lymphocyte Count
BMI	$r = .212$	.389	.286	.253	.113
	$p = .076$	.001*	.016*	.033*	.349
Triceps skinfold (% of median)	$r = .209$	.261	.059	.259	.195
	$p = .087$	.032*	.633	.033*	.111
Midarm muscle area (% of median)	$r = .234$	.282	.321	.205	.005
	$p = .055$	.020*	.008*	.093	.967
Midarm circumference (% of median)	$r = .187$	.291	.241	.177	.055
	$p = .127$	.016*	.048	.148	.658
Calorie count	$r = .081$	.113	.170	.254	.099
	$p = .536$	.390	.193	.050*	.451

*Statistically significant at $p < .05$.

Many plasma protein levels are altered in the course of infectious disease and stress. Serum albumin, prealbumin, and transferrin are negative acute phase reactants and therefore decrease during the acute phase response (APR). Genes associated with the APR are regulated by TNF, IL-1, and IL-6 (23,24). Several studies have evaluated the relationship between these cytokines and serum proteins. Henning et al. (25) found that rabbits infused with TNF developed hypoalbuminemia. This was thought to be due to TNF-induced endothelial cell injury resulting in increased endothelial permeability to albumin. In another study, mice given a monocyte product (crude secretory products of stimulated monocytes) and IL-1 had a significant decrease in plasma albumin (26). Elevated levels of IL-6 were associated with reduced serum albumin in a study of cancer patients (27). Human hepatocytes incubated with IL-6 reduced albumin synthesis by 50% (28,29). IL-2 does not play a key role in the APR. However, infusion of IL-2 in cancer patients lowers serum albumin (30). The relationships between sIL-2R and albumin, prealbumin, cholesterol, and transferrin have not been previously studied.

Soluble IL-2R levels increase with cancer, autoimmune disease, infection, and age (31). The mechanism of this increase is not well understood. Whether sIL-2R has a direct effect on tissues or merely reflects IL-2 activity is also not known. It is interesting to note that the ability to produce IL-2 and sIL-2R in response to stimulation declines with age (32).

Although many researchers have questioned the value of serum albumin in diagnosing malnutrition in hospitalized patients, it is still commonly used (4,6,13,17). Both albumin and cholesterol are components of the Nutrition Screening Initiative (9), and albumin and total lymphocyte count are part of most VA Medical Center assessments. The Mini Nutritional Assessment (developed and used primarily in Europe) does not include laboratory measurements (33). Careful diagnosis of malnutrition is important because this is a treatable condition. Conversely, it may be inefficient to supply nutritional support to patients who are not actually malnourished.

There are several limitations to this study. First, the sample size of 72 is small. Second, activity of the immune system is complex and difficult to ascertain. Serum levels of cytokines may not reflect tissue activity. Some cytokines assayed are often not detectable in normal samples and, therefore, may not be good indicators of subacute inflammation. For some cytokines (particularly IL-6), the kit used may not have been adequately sensitive. Third, the exact nature and role of sIL-2R is not yet well understood. Although our correlation shows an association between nutritional markers and sIL-2R, further studies are required to demonstrate that inflammation is a cause of low nutritional markers. Finally, this study was limited to older hospitalized men. Further studies will be needed to test the relationship between sIL-2R and biochemical indices in other populations.

To our knowledge this is the first study to find a relationship between sIL-2R and albumin, cholesterol, prealbumin, and transferrin. Because all of these markers are hepatically produced, we speculate that IL-2 or sIL-2R affect hepatic metabolism.

In conclusion, this pilot study suggests that the presence of inflammation may increase the incidence of hypoalbuminemia and hypocholesterolemia, potentially leading to an overdiagnosis of malnutrition in hospitalized patients. We suggest that these markers be interpreted with caution in the nutritional assessment of older hospitalized patients. In the future, inflammation might be factored out of serum nutritional markers such as albumin, prealbumin, and cholesterol, which could make the diagnosis of malnutrition more accurate. Albumin, cholesterol, and hemoglobin are common laboratory tests not just used to diagnose malnutrition. Interpretation of these tests should be made with the understanding that they may be influenced by inflammation. Further study will improve our knowledge of the impact of inflammation on albumin, prealbumin, transferrin, hemoglobin, and cholesterol.

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APPENDIX A

Nutritional Status

Subjective factors (appetite, dietary history, swallowing problems. etc.), as well as unintentional weight loss, percent ideal body weight, diet, diagnosis (e.g., gastrointestinal disorder, cancer, diabetes, renal failure), albumin, and total lymphocyte count are assigned scores by the dietitian. Patients are assigned categories to include; no compromise, mild, moderate, and severe compromise.

APPENDIX B

Nutritional Class

A. Kwashiorkor (severe protein deficiency). Diagnosis must meet criterion number one plus two of the other criteria listed.

1. Serum albumin <25 g/L.
2. TLC <800 mm^3 (exclusions: currently receiving radiation or chemotherapy, 1 month post-radiation or chemotherapy, currently receiving immunosuppressant medication, sepsis).
3. Normal or increased weight for height or weight maintained.
4. Normal or increased fat and muscle stores, if measured with skinfold calipers.
5. Pitting edema.

B. Nutritional marasmus. Diagnosis must meet all criteria listed.

1. Weight ≤80% of ideal body weight (IBW) or documented unscheduled weight loss of ≥10% usual weight in past 6 months.
2. Depressed somatic protein stores and adipose stores (i.e., overt signs of wasting by prominence of body skeleton, especially with extremities and chest cavity).
3. Serum proteins maintained (serum albumin >30 g/L; TLC >1200 mm^3).

C. Other severe protein calorie malnutrition (combined maras-mus-kwashiorkor). Diagnosis must meet all criteria listed.
   1. Weight ≤80% of ideal body weight or documented unscheduled weight loss of ≥10% usual weight in past 6 months.
   2. Depressed visceral protein status (serum albumin <30 g/L; TLC <1200 mm³, exclusions are listed under kwashiorkor).
   3. Depressed somatic protein and adipose stores.

D. Unspecified protein-calorie malnutrition.
   1. Nutrition assessment supports some type of malnutrition, but sufficient laboratory and anthropometric data to specify type of malnutrition are not available.
   2. As available, nutritional and medical histories, biochemical values, clinical judgement, and other data will be utilized in the determination of this nutritional deficiency.

Call for Nominations

The PGC Polisher Research Institute Award of The Philadelphia Geriatric Center

The Gerontological Society of America invites nominations for
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Purpose

The award recognizes a significant contribution in gerontology that has led to an innovation in gerontological treatment, practice or service, prevention, amelioration of symptoms or barriers, or a public policy change that has led to some practical application that improves the lives of older persons.

Eligibility

The award may be given to a person from any discipline who has made such a contribution to applied gerontology. Nominations must be made or endorsed by a member of The Gerontological Society of America although nominees need not be members of GSA.

Nominating Process

Contact GSA's Awards Coordinator at 202/842-1275 or FAX 202/842-1150 for a list of criteria and a Nomination Form to be submitted with appropriate accompanying materials to:

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Nominations must be received by May 8, 1998.