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Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure

Chamberlain I. Obialo, Eni C. Okonofua, Magnus C. Nzerue, Arti S. Tayade, and Louis J. Riley

Renal Section, Department of Medicine, Morehouse School of Medicine, Atlanta, Georgia, USA

Role of hypoalbuminemia and hypocholesterolemia as co-predictors of mortality in acute renal failure.

Background. Hypoalbuminemia (LA) and hypocholesterolemia (LC) have been reported to portend high mortality in both older patients and in patients with end-stage renal disease. Even though low levels have been reported in critically ill patients, they have not been clearly defined as predictors of mortality in acute renal failure (ARF). The impact of LA and LC on mortality in ARF is evaluated in this study.

Methods. We conducted a computer-assisted three-year retrospective review of all cases of *de novo* ARF seen at an inner city tertiary-care facility. One hundred cases met the criteria for inclusion in the study. We employed both univariate and multivariate logistic regression models to estimate the relative risks (RR) and 95% confidence intervals (CI) of mortality associated with several variables.

Results. Predictors associated with a high risk of death identified in this study include LC ≤ 150 mg/dl (≤ 3.9 mmol/liter; RR, 7.4; CI, 2.7 to 20.3), LA ≤ 35 g/liter (RR, 5.0; CI, 1.9 to 13.2), sepsis (RR, 9.4; CI, 3.7 to 23.9), mechanical ventilation (RR, 10.8; CI, 2.8 to 41.0), oliguria (RR 17.0; CI, 6.2 to 46.6), and multisystem organ failure (RR 24.7; CI, 10.3 to 59.1). The overall gross mortality was 39%, but mortality among intensive care unit patients was 82%. Survival was 82% among patients with serum albumin > 35 g/liter versus 48% among those with serum albumin ≤ 35 g/liter ($\chi^2 = 11.9$, $P = 0.0006$). Similarly, survival was higher among patients with cholesterol > 150 mg/dl (> 3.9 mmol/liter) than those whose levels were ≤ 150 mg/dl (≤ 3.9 mmol/liter; 85 vs. 44%, $\chi^2 = 17.3$, $P < 0.0001$). Significant association between LA and LC was observed ($R = 0.4$, $P < 0.0001$). Age, gender, level of plasma creatinine, and underlying chronic medical conditions were not predictive of mortality.

Conclusion. Survival in ARF is significantly altered by the levels of albumin and cholesterol. Because both LC and LA can be cytokine mediated, their presence in ARF should be considered ominous.

Key words: end-stage renal disease, renal insufficiency, mortality prediction, cholesterol, albumin, risk factors for death.

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Mortality associated with acute renal failure (ARF) remains high despite recent advances in critical care medicine, renal replacement therapy, use of biocompatible dialysis membranes, and nutritional support. The mortality rates vary from 25 to 90% depending on the severity of illness and hospital setting [1–7]. The use of logistic regression models has enabled many investigators to estimate the risks of mortality associated with numerous outcome predictors. The major adverse outcome predictors are: sepsis, underlying disease, multiorgan dysfunction state (MODS), oliguria, hyperbilirubinemia, mechanical ventilation, cardiovascular complications, and severity of illness, as assessed by use of Acute Physiology and Chronic Health Evaluation Scores (APACHE) [1, 4, 7].

Although hypoalbuminemia (LA) and hypocholesterolemia (LC) have been reported to be independent predictors of high mortality in both older patients and patients with end-stage renal disease (ESRD) [8–11], there is paucity of information in the literature concerning the presence or absence of an association between LA and LC with mortality in ARF. Hypoalbuminemia was recently reported by Chertow et al as a predictor of mortality with a relative risk (RR) of 0.56 in their patients with acute tubular necrosis (ATN) [1]. In this study, we identified several previously reported predictors of mortality in ARF and confirmed their association with mortality, but, in addition, observed a consistent association between hypoalbuminemia and hypocholesterolemia with mortality. The effect of LA and LC on mortality in *de novo* ARF has not been previously reported, to our knowledge. Patients with pre-existing renal insufficiency were excluded so that any underlying LA and LC would not constitute confounding variables.

METHODS

The Grady Memorial Hospital (Atlanta, GA, USA) is a 900-bed tertiary- and secondary-care medical center that serves metropolitan Atlanta. Using its comprehensive medical information retrieval system, we conducted

a three-year (1994 to 1996) computer-assisted retrospective review of all hospital discharges classified as ARF, renal failure, ATN, and acute tubulointerstitial nephritis. Two hundred and forty cases of ARF were identified, and their charts were retrieved and reviewed in depth.

Exclusion criteria were: age ≤18; all obstetric related cases of ARF, pre-existing chronic renal insufficiency with serum creatinine ≥1.7 mg/dl (150 μmol/liter); all cases documented as acute-on chronic renal failure; all cases of glomerulonephritis; and all patients whose elevation in serum creatinine resolved within 48 hours. Patients with incomplete records and those who left the hospital prematurely without follow-up arrangements were also excluded.

Inclusion criteria were as follows: serum creatinine elevation of at least 0.5 mg/dl (44 μmol/liter) and ≥2.0 mg/dl (177 μmol/liter) when baseline value was <1.7 mg/dl (150 μmol/liter) and serum creatinine ≥2.0 mg/dl (177 μmol/liter) at the time of presentation when no prior history of ARF was available.

A total of 100 of the 240 ARF cases satisfied the criteria for inclusion in this study. Demographic, biochemical, and clinical profiles of all patients were noted. Sepsis was considered to be present when positive blood cultures were documented with or without elevated temperature ≥ 38°C and/or presence of hypotension. Oliguria was defined as urine output of ≤400 ml/day. Multiple organ dysfunction state (MODS) was considered present when ARF was coupled with several other dysfunctional organ systems such as respiratory failure with the use of mechanical ventilation or decreased $PO_2/FI0_2$ ratio; liver failure (with elevated bilirubin and transaminases), coma, or seizure disorder; myocardial infarction, use of multiple pressors for cardiovascular support and dysrhythmias; and hematologic dysfunction with coagulopathy, anemia, and or thrombocytopenia. The scoring of MODS was based on modification of the format designed by Marshall et al [12]. An all-or-none semiquantitative score derived from the intensive care unit (ICU) admission value and cumulative values over entire ICU stay were used for analysis (Δ MODS). Patients with scores ≥12 or ≥3 organ system involvement were classified as MODS for comparative analysis. No comparison was made between various scores and mortality.

Analysis

Continuous variables are reported as mean ± SD. Chi square (χ^2) was used for intragroup comparison of nominal variables. Univariate logistic regression analyses were performed on 17 independent variables to explore their effect on the outcome of interest, which in this study was "mortality." These variables included age, gender, serum creatinine, serum albumin, cholesterol and electrolytes, sepsis, use of mechanical ventilation, oliguria, MODS, and underlying medical history. Variables with significant association (at $P < 0.05$) were re-analyzed using a multivariate logistic regression model. Variables were included by an automated format. Goodness of fit statistics were based on a comparison of the model to a saturated model that allowed outcome variable to vary arbitrarily over all distinct levels of the independent variables. Final step selections were based on a model fit that yielded a likelihood ratio with a P value < 0.05. Model discrimination or the ability to distinguish patients who died from those who survived was based on an automated estimated probability of mortality using a prior probability of 0.5 and a 2×2 logistic classification table, which corresponded to the receiver operating characteristic curve (ROC), as described by Lemeshow and Le Gall [13]. Coefficient of binary variables and their standard errors were used to calculate the RRs of death and their 95% confidence interval (95% CI). Censoring of events was made at 120 days based on a 90-day maximum hospital stay plus a 30-day posthospital discharge follow-up. Kaplan–Meier survival plots were employed to show survival trends associated with both hypoalbuminemia and hypocholesterolemia. The software package "Statview" (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Table 1. Demographic, clinical and select laboratory profiles of the study patients

Characteristic	Value
Age *years*	53.7 ± 19.9
Gender *M, %*	65
Seight *kg*	65.1 ± 15.8
MAP *mm Hg*	87.3 ± 19.6
Peak plasma creatinine *mg/dl (μmol/liter)*	5.6 ± 3.9 (445 ± 344.8)
Albumin *g/liter*	31 ± 8
Cholesterol *mg/dl (mmol/liter)*	148.3 ± 51.8 (3.9 ± 1.4)
Sepsis %	45
Oliguria %	40
Dehydration %	49
Dialysis %	10
MODS %	32
Mortality %	39

Abbreviations are: MODS, multiple organ dysfunction states; MAP, mean arterial pressure.

RESULTS

All of the patients in this study were African Americans aged 20 to 93 years. Thirty-five percent of the patients were ≤40 years old, whereas 38% were ≥64 years old. Table 1 lists many of the demographic and clinical profiles of the patients. The reported albumin, cholesterol, and mean arterial pressure (MAP) levels represent readings obtained at admission. The serum albumin ranged from 13 to 49 g/liter, whereas the cholesterol ranged from 58 to 290 mg/dl (1.5 to 7.5 mmol/liter). The serum creatinine ranged from 2.0 to 22 mg/dl (177 to 1944.8 μmol/liter). Ten percent of the patients required

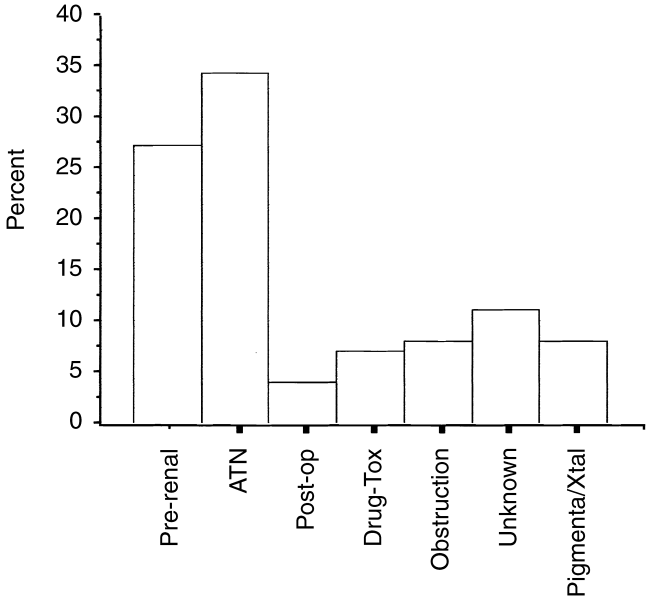

Fig. 1. Histogram showing the documented etiology of acute renal failure. Abbreviations are: Post-op, postoperative acute tubular necrosis (ATN); Drug Tox, all nephrotoxin-mediated causes such as contrast and aminoglycosides; Xtal, all crystal-related causes.

Table 2. Univariate analysis of select possible predictors of mortality

Variable	RR	CI	*P* value
Underlying history of CHF	0.05	0.01–0.5	0.01
Gender	0.67	0.29–1.56	0.35
Plasma creatinine ≥*3.0 mg/dl (≥265.2 μmol/liter)*	0.7	0.3–1.6	0.3
Age	1.01	0.99–1.03	0.27
Albumin ≤*35 g/liter*	5.0	1.9–13.2	0.001
Cholesterol ≤*150 mg/dl (≤3.9 mmol/liter)*	7.4	2.7–20.3	<0.0001
Sepsis	9.4	3.7–23.9	<0.0001
Mechanical ventilation	10.8	2.8–41.0	0.0005
Oliguria	17.0	6.2–46.6	<0.0001
MODS	24.7	10.3–59.1	<0.0001

Abbreviations are: MODS, multiple organ dysfunction states; CI, 95% confidence interval; RR, relative risk; CHF, congestive heart failure. Variable are arranged in increasing order of RR.

dialysis; however, 50% of those who were dialyzed died. The overall mortality was 39%, but 14 of 17 patients (82%) admitted to the ICU expired. The causes of ARF as documented in the charts are shown in Figure 1. Sixty percent of the cases resulted from intrarenal causes; 30% were prerenal, and 10% were postrenal.

Outcome

The main outcome of interest in this study was mortality. Table 2 shows the results of the univariate analysis and the RR of mortality associated with various characteristics. Age, gender, and plasma creatinine levels did not portend adverse outcome. The mean plasma creatinine level in survivors was 5.9 ± 4.4 mg/dl (521.6 ± 389 μmol/liter), and the mean difference in serum creatinine levels between survivors and nonsurvivors was +0.7 mg/dl (62 μmol/liter, $P = 0.4$). The underlying medical conditions did not contribute significantly to mortality except in patients with congestive heart failure (CHF) in whom six of seven (86%) expired, and in patients with chronic obstructive pulmonary disease (COPD) in whom two of three (67%) also expired. We were unable to show any definite relationship between age, electrolyte abnormalities, and mortality. Patients with Acquired Immunodeficiency Syndrome (AIDS) were generally ≤40 years old, but only 12 of 27 (44%) died. Multiorgan failure carried the highest RR of death. Multivariate logistic regression analysis revealed that MODS was the most important predictor of mortality. In the presence of MODS, the RR of death associated with all other variables was reduced and not significant. However, when MODS was excluded from analysis, hypoalbuminemia ≤35 g/liter, hypocholesterolemia ≤150 mg/dl (≤3.9 mmol/liter), presence of sepsis, and oliguria were predictive of high mortality (Table 3). Although the RR of death associated with LA was high, it did not attain a significant *P* value in multivariate analysis. However, the likelihood ratio test attained a *P* value of <0.05, and hence it is included in Table 3. Further analysis of patients with sepsis revealed that 52% had cholesterol <150 mg/dl (3.9 mmol/liter) as compared to 47% with cholesterol >150 mg/dl (3.9 mmol/liter, $P = 0.2$). Similar analysis for albumin showed that 53% of septic patients versus 46% of nonseptic patients had an albumin level <35 g/liter ($P = 0.1$). Using a prior probability of 0.5, our model classification yielded a total correct classification of 83% (data not shown).

Table 3. Multivariate proportional hazard analysis of predictors of high mortality in the absence of MODS

Variable	RR	CI	χ^2	*P* value
Albumin ≤*35 g/liter*	3.6	0.9–14.4	3.4	0.06
Cholesterol ≤*150 mg/dl (≤3.9 mmol/liter)*	4.7	1.3–16.9	5.7	0.02
Sepsis	5.5	1.7–18.1	7.8	0.005
Oliguria	11.9	3.5–40.1	15.9	<0.0001

Abbreviations are in Table 2 legend.

Figures 2 and 3 show the relationship between LA and LC with survival. The mean albumin level among patients who died was 27 ± 7 g/liter as compared with 34 ± 7 g/liter in survivors ($P < 0.0001$). At censoring, 82% of cases with albumin >35 g/liter were alive compared with 48% of those with albumin ≤35 g/liter ($\chi^2 = 11.9$, $P = 0.0006$). The mean cholesterol level among nonsurvivors was 121.2 ± 34 mg/dl (3.2 ± 0.9 mmol/liter) vs. 165.6 ± 54 mg/dl (4.3 ± 1.4 mmol/liter) in survivors ($P < 0.0001$). Also, at censoring, 85% of cases with cholesterol >150 mg/dl (>3.9 mmol/liter) were alive compared with 44% of those with cholesterol ≤150 mg/dl

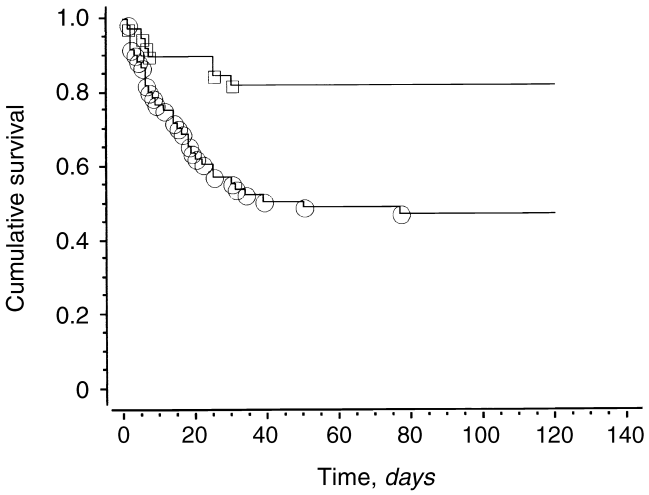

Fig. 2. Kaplan–Meier cumulative (Cum) survival plot for serum albumin. Symbols are: (□) event times in patients with albumin > 35 g/liter; (○) albumin ≤ 35 g/liter.

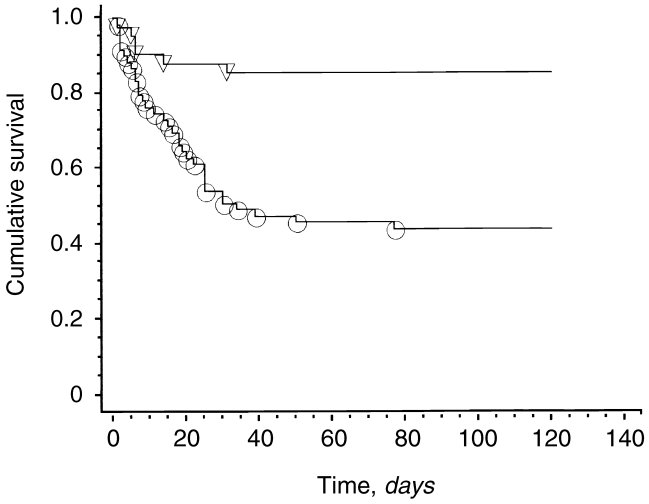

Fig. 3. Kaplan–Meier survival plot for cholesterol. Symbols are: (▽) event times in patients with serum cholesterol > 150 mg/dl; (○) cholesterol ≤ 150 mg/dl (≤ 3.9 mmol/liter).

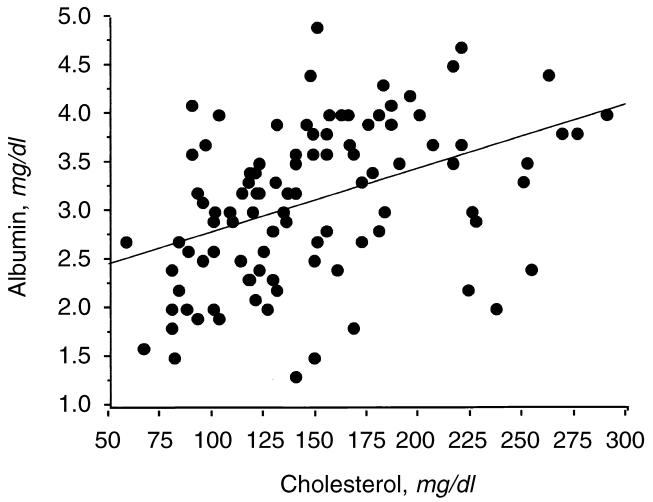

Fig. 4. Regression plot showing the association between cholesterol and albumin ($Y = 2.13 + 0.007X$; $R^2 = 0.18$).

(≤3.9 mmol/liter, $\chi^2 = 17.3$, $P < 0.0001$). Figure 4 displays the association between albumin and cholesterol ($R = 0.4$, $P < 0.0001$).

DISCUSSION

This study primarily involved patients with *de novo* ARF and sought to identify factors that were predictive of high mortality. We have confirmed previously published observations concerning the role of oliguria, sepsis, MODS, ICU stay or mechanical ventilation and cardiovascular complications as predictors of high mortality in ARF [1, 4–7]. Multiple organ failure was the most significant predictor of mortality and essentially overshadowed the risks associated with other factors. The literature is replete with reports identifying age and gender as either predictors [6, 7] or nonpredictors of mortality [1, 2, 14]. We were unable to show age as a risk factor for mortality. Like other investigators, we observed a male predominance in the incidence of ARF [1, 6, 7, 14] but were unable to show male gender as a risk factor for mortality. The role of gender as an adverse outcome predictor remains questionable. A recent study reported a male gender-related mortality RR of 2.0 [1].

A plasma creatinine level ≥ 3.0 mg/dl (≥ 265.2 μmol/liter) [2] has been reported to be predictive of high mortality in ARF. In contrast, high serum creatinine levels have been associated with lower mortality risk in patients with ESRD [15], whereas ESRD patients with low serum creatinine concentrations have higher mortality [9]. We were unable to relate the creatinine level to mortality in this study even when patients with serum creatinine < 3.0 mg/dl (265.2 μmol/liter) were excluded from analysis. Indeed, the mean difference in plasma creatinine levels between survivors and nonsurvivors was not significant. Low plasma creatinine levels may be observed in advanced renal failure as a result of decreased muscle mass, malnutrition, advanced age, and chronic liver disease. It is not surprising, therefore, that the creatinine level often bears no obvious hazard risk in ARF.

The high mortality associated with LA in patients with ESRD has been well documented [8–10, 15], but its role in ARF has not been clarified. In a study involving over 15,000 acutely ill patients, admission serum albumin < 34 g/liter was reported to be a strong predictor of mortality, prolonged length of stay, and readmission [16]. Of note, ARF was not included as a variable associated with in-hospital death in that study. It was not until recently that Chertow et al reported that LA was associated with an

RR of 0.56 with respect to mortality or dialysis in their patients with ARF [1]. Our study is in agreement with their findings, although we observed a much higher RR of death when we employed both univariate and multivariate logistic regression analysis. The albumin level is generally regulated by dietary protein intake; hence, most studies in ESRD patients have concluded that LA is a consequence of visceral protein malnutrition. In experimental models, renal failure *per se* neither suppresses albumin synthesis nor results in a reduced albumin pool [17, 18]. However, accelerated protein breakdown is a hallmark of metabolic alterations in ARF. Protein catabolism in this setting has been attributed to the acute disease process, uremic toxins, inflammatory mediators, metabolic acidosis, circulating proteases, hormonal imbalance, and insulin resistance among other factors [19]. Albumin has been demonstrated to be a negative acute-phase reactive protein; that is to say, its synthesis is suppressed in response to inflammatory conditions [20]. Kaysen, Stevenson, and Depner examined the relationship between serum albumin and serum levels of two positive acute-phase proteins, c-reactive protein (CRP) and serum amyloid A (SAA) in 115 hemodialysis patients [21]. In confirmation of the earlier observation, they found that both CRP and SAA were inversely related with albumin.

Hypocholesterolemia has also been reported to be a predictor of high mortality in ESRD [10] and in the older population [11, 22]. However, the relationship between LC and noncardiovascular-related mortality remains unresolved [23]. Concentrations of total cholesterol have been reported to be reduced as part of an acute-phase response analogous to that of albumin in hemodialysis patients [24]. Hypocholesterolemia and low high-density lipoproteins (HDLs) [25] have been described in critically ill surgical ICU patients with evidence of sepsis. Subsequent to experiments that suggested that lipoproteins play a role in binding and neutralization of endotoxin [26], Gordon et al suppressed lipopolysaccharide-stimulated production of tumor necrosis factor-α (TNF-α) by infusion of reconstituted HDL preparation into their septic patients [25]. Although these authors did not correlate survival with lipid concentrations, a recent report [24] found a significant relationship between both tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and the degree of LA and LC in their patients. They observed that IL-6 was the strongest predictor of mortality. In a recent study, we observed that LA and LC were highly predictive of mortality. It is provocative that albumin and cholesterol levels showed a weak but highly significant association, implying commonality in their etiology. This commonality may be related to nutrition, uremic toxins, or inflammatory mediators. Sepsis appeared to be an unlikely factor because we were unable to show a significant correlation between the combination of LA and LC with sepsis.

We recognize that some concerns exist regarding this study, which include: the low percentage of patients requiring dialysis, our inclusion criteria for ARF with a lower creatinine [that is, ≥2.0 mg/dl (177 μmol/liter)] than other studies have used, and the fact that all study patients were African Americans living in an inner city locale. The need for dialysis among patients with ARF is variable. Studies report a range of incidence rates from 36% [27] to a range of 46 to 86% in a study of predominantly ICU patients [6]. Our comparatively low rate of 10% reflects the inclusion of a significant number of patients with metastatic neoplastic conditions, severe cardiomyopathy, and terminal AIDS who were either not offered or who refused dialysis. Family members of such patients as well as the patients were involved in all aspects of the decision to withhold dialysis. There is no consensus about either the level or the rate of rise of creatinine that constitutes ARF. Chertow et al selected a creatinine change of ≥1.0 mg/dl (88 μmol/liter) [1], whereas Brivet et al chose a level ≥3.5 mg/dl (308 μmol/liter) [6]. Of note, many studies have used a creatinine level of ≥2.0 mg/dl (177 μmol/liter) as the defining criterion for ARF [27–29] in keeping with our criterion. Finally, the ethnic origin and implied socioeconomic status of our patients should not alter the findings in this study. With the exception of LA and LC, all other predictors of mortality in ARF identified in this study have been well documented [1, 4, 7]. There is no reason to suspect that LA and LC are unique to African Americans. A review of data from the National Center for Health Statistics revealed that serum albumin was positively correlated with serum cholesterol and, furthermore, that other cardiovascular risk factors correlated with serum albumin in both whites and blacks [30].

We believe that our findings are timely and should stimulate further prospective examination with better indices of nutritional status in a more diverse ethnic population. The presence of LA and LC in patients with ARF should be seriously considered among factors other than merely evidence of poor nutrition alone as impetus for more aggressive management of patients. However, the extent that both LA and LC may reflect poor nutritional status, the effects of which are well known to be associated with higher morbidity and mortality in hospitalized patients, warrants aggressive nutritional repletion and supplementation.

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Reprint requests to Chamberlain I. Obialo, M.D., Department of Medicine, Morehouse School of Medicine, 720 Westview Drive, S.W., Atlanta, Georgia 30310, USA.

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