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Research Article

Serum Albumin as an Independent Predictor of Mortality among Older Veterans Discharged from Recuperative Care

Lana M Brown[1,3]*, Shelly Y Lensing[1,3], Paula K Roberson[1,3], Melinda M Bopp[1] and Dennis H Sullivan[1,4]

[1]*Geriatric Research Education and Clinical Center (GRECC), USA*
[2]*College of Nursing, University of Arkansas for Medical Sciences, USA*
[3]*Department of Biostatistics, University of Arkansas for Medical Sciences, USA*
[4]*Department of Geriatrics, University of Arkansas for Medical Sciences, USA*

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***Corresponding author**

Lana M Brown, PhD, RN, Central Arkansas Veterans Healthcare System, 2200 Fort Roots Drive, 3J/NLR, North Little Rock, AR 72114,USA,
Tel: 501-257-2075; Fax: 501-257-2501;
Email: Lana.brown2@va.gov

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Abstract

Background: Incident Serum Albumins (SA) have been extensively studied as a prognostic indicator in community-dwelling and hospitalized older adults, but less is known about the association between SA and long-term outcomes among older patients admitted to a Recuperative Care and Rehabilitation Unit (RCRU).The study purpose was to examine the association between SA obtained at discharge from a RCRU and the risk of mortality over the subsequent 9.2 years.

Methods: This prospective cohort studyincluded383 older Veterans (mean age = 78.6±7.6 years, 98% male, and 87% white) who were discharged alive and in stable medical condition from a Department of Veterans Affairs Community Living Center RCRU with outpatient follow-up. At discharge, each subject completed a comprehensive assessment and was then monitored as an outpatient for up to 9.2 years. Associations between SA at RCRU discharge and mortality were identified utilizing Cox proportional hazards (PH) regression analyses adjusting for conditions known to confound this relationship.

Results: The mean (SD) discharge albumin was 3.3 g/dL (0.4). During the study, 255 subjects (67%) died. The risk of death for those with albumin <3.0 vs. >3.4 was 3.1 times higher at year 2 (HR=3.09 [95% CI, 2.14, 4.48], p<0.001), but by year 3 the risk of death between the two groups was no significant (HR=1.41 [95% CI, 0.97-2.05], p=0.074).

Conclusions/Implications: Among older Veterans, SA obtained at discharge from a RCRU is significantly associated with the risk of mortality over the subsequent two years. Veterans with a low RCRU discharge SA may need more aggressive monitoring and care during this period of increased mortality risk.

Introduction

Incident Serum Albumins (SA) have been extensively studied as a prognostic indicator in community-dwelling and hospitalized older adults. A meta-analysis showed the SA mean value for community-dwelling older adults was 4.1 g/dL and for hospitalized older adults was 3.6 g/dL [1]. Studies of community-dwelling older adults consistently demonstrate a strong inverse association between SA and the risk of mortality with a clear risk gradient demonstrated even within the reference range for SA [1-5]. Further, the incident SA remains significantly associated with mortality risk throughout the subsequent 12 years [1-4]. In contrast, studies of hospitalized older adults indicate that SA is an indicator of short-term mortality risk. In this setting, a strong inverse association has been identified between SA and the risk of mortality during the hospitalization and for up to 12 months post-discharge [1,6-9]. SA has not been shown to be a predictor of long-term survival among hospitalized patients [1,9]. This finding is consistent with the fact that SA is a negative acute phase reactant and that its concentration drops in response to acute inflammatory conditions; in this sense, SA has been considered an indicator of illness severity among hospitalized older adults and may not reflect an individual's baseline health status [1,9].

Less is known about the association between SA and long-term outcomes among older patients admitted to a Recuperative Care and Rehabilitation Unit (RCRU). As patients admitted to a RCRU are generally in the recuperative phase of an acute illness, their SA concentrations at discharge may reflect their rate of recovery rather than what will become their new post-acute illness baseline health status and thus long-term prognosis. Studies of older adults discharged from a RCRU demonstrate a strong inverse association between discharge SA and mortality within the subsequent year; it is not known whether this relationship remains significant over a longer period of follow-up [1,10-12].

The purpose of this study was to investigate this issue. This issue is important because many frail older adults discharged from a RCRU have good long-term prognosis despite SA levels that are considered clinically abnormally low compared to community-dwelling older adults [1,13]. The association between low SA levels and long-term mortality in this population is not known.

Methods

Patients aged 65 years and older admitted to a RCRU of a university-affiliated Department of Veterans Affairs Community Living Center (CLC) was evaluated for enrollment in this prospective study between March 2006 and March 2010. Patients being admitted for respite or long-term custodial care or having a terminal disease were excluded from study participation. There were 540 patients who met study eligibility criteria with 446 agreeing to enter the study. Written informed consent was obtained from all subjects or from a legal representative if the subject lacked adequate decision-making capacity. Of those enrolled, 21 withdrew, four subjects died during their stay, two lacked laboratory data, and 36 were discharged in an unstable condition to an acute care hospital. The remaining 383 subjects were discharged in a stable condition and represent the study population. The study was compliant with the regulations and ethical standards of the Declaration of Helsinki, Health Insurance Portability and Accountability Act, Department of Veterans Affairs, and the Institutional Review Board of the Central Arkansas Veterans Healthcare System.

The RCRU study and study population are described in further detail elsewhere [10,13,14]. Subjects received comprehensive medical, neuropsychologic, nutritional, functional, social, and metabolic evaluations on a regularly scheduled basis during their stay and, if possible, on the day of discharge. After discharge from the RCRU, these subjects were followed through phone calls, clinic visits, and medical record review until their death or through July 15, 2015.

Albumin was measured using turbidimetric immunoassay using the Beckman Coulter SYNCHRON LX System, UnicelDxC 800 System, and SYNCHRON System Protein Calculator (Brea, CA). Discharge clinical data for SA concentrations in the study population was defined as 'normal' based on the standard reference range of 3.4-5.0 g/dL used by the hospital laboratory. Discharge SA levels were segregated into three groups: SA ≤ 3.0, 3.1 to 3.3, and ≥ 3.4 g/dL. The cut point of 3.0 g/dL was chosen as it corresponds to the 25th percentile, and ≥3.4 g/dLis above the hospital's clinical threshold for hypoalbuminemia.

Albumin levels can be influenced by and have prognostic implications for a number of potentially serious chronic conditions including Congestive Heart Failure (CHF), chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hypertension, and diabetes mellitus [1,9,15-18]. Based on the medical evaluation, variables were created to indicate the presence or absence of each of the various conditions to be investigated as potential confounders of the association between SA and mortality. Body Mass Index (BMI) was investigated as the indicator of nutritional status, and grouped as ≤18.4, 18.5-29.9, and ≥30 kg/m^2 based on the criteria of the U.S. Department of Health & Human Services [19]. Age was categorized as 65-74, 75-84, and ≥85 years.

Statistical analysis

Descriptive statistics were used to summarize study subjects' characteristics. Cox proportional hazards (Cox PH) regression was used to assess the association between SA and long-term mortality [20]. Participants who were still alive at last follow-up were right censored. The initial model included SA group as the independent variable and age group, BMI group, and discharge diagnoses as covariates. Variables significant at $p<0.10$ were maintained in the final model. Since the Cox PH model assumes that the hazard function for independent variables remains proportional over time (i.e., constant relative hazard), the supremum test [21] was used to assess proportional hazards. Since this test rejected proportional hazards for discharge albumin, the interaction between albumin and log time was included in the Cox model and hazard ratios were also estimated at specific time points to investigate how the impact of discharge albumin changed over time; the model without the interaction is also presented as it reflects the average effect of albumin over time. Analyses were conducted using SAS Enterprise Guide software (version 5.1, SAS Institute, Inc., Cary, NC). Significance was defined as a two-tailed $p < 0.05$.

Results

The majority of the 383 study participants were male (98%) and white (87%) with a mean age of 78.6 ± 7.6 years. The mean (SD) discharge albumin was 3.3 g/dL (0.4) and ranged from 1.8 to 4.6 g/dL. Only 11 (2.9%) participants had albumin levels at or above 4.1 g/dL, which is generally the average seen in healthy populations [1]. Additional characteristics of the study subjects according to discharge SA are shown in Table 1 [22]. Patient characteristics did not significantly differ according to discharge SA. Surviving patients were followed a median (range) of 6.3 (0.1-9.2) years. From hospital discharge to study end, 255 (67%) of the subjects were known to have died. Within the first year after discharge, 64 subjects (17%) died. In total, 27 subjects (7%) were lost to follow-up a median of 3.1 years after discharge.

Figure 1 shows the Kaplan-Meier estimates of survival according to discharge SA. At 3 years, the Kaplan-Meier survival estimates were 67.5% (95% CI, 60.1-73.8%), 56.0% (95% CI, 45.6-65.2%), and 46.2% (95% CI, 36.0-55.8%) for highest, middle, and lowest discharge albumin groups, respectively. Table 2 shows the results of the final Cox PH main effects model, which examines the average effect of albumin over time. Subjects with a discharge albumin ≤3.0 had a 41% increase in the risk of death as compared to those with albumin ≥3.4 (HR 1.41, [95% CI, 1.04-1.92], p=0.029) after adjusting for age, BMI, and CHF diagnosis at discharge. Albumin 3.1 to 3.4 did not confer a significantly higher risk of death as compared to those at or above reference (HR 1.20, [95% CI, 0.88 - 1.62], p=0.247). Additionally, age 85 and older, BMI<18.5, and CHF diagnosis were associated with higher risk of death.

In the Cox PH model, all of the variables met the proportional hazards assumption, except for the indicator variable for albumin ≤3.0 ($p<0.001$). Therefore, we included an interaction term between albumin ≤3.0 and $\log_e$ (time). Low albumin at discharge was still significant, but with decreasing impact over time. The risk of death for those with albumin ≤3.0 vs. ≥3.4 was 3.1 times higher at year 2 (HR=3.09 [95% CI, 2.14, 4.48], $p<0.001$) after adjusting for age, BMI, and CHF; by year 3 the risk of death between the two groups was nonsignificant (HR=1.41 [95% CI, 0.97-2.05], p=0.074) and at later

Table 1: Characteristics of Study Subjects according to Discharge Albumin.

Variable	Discharge Albumin (g/dL) ≤3.0 (n=100)	3.1-3.3 (n=99)	≥3.4 (n=184)	P-value[a]	All Subjects (n=383)
Age, years, mean± SD	79.3 ± 6.9	77.7 ± 8.0	78.8 ± 7.7	0.302	78.6 ± 7.6
Male, n (%)	99 (99)	96 (97)	182 (99)	0.495	377 (98)
White race, n (%)	88 (88)	84 (85)	160 (87)	0.805	332 (87)
Smoker, n (%)	11 (11)	16 (16)	26 (14)	0.596	53 (14)
Body Mass Index, admission, kg/m^2, mean± SD[b]	25.5 ± 5.3	26.3 ± 5.7	26.5 ± 5.3	0.311	26.3 ± 5.6
A discharge diagnosis of:					
Congestive Heart Failure, n (%)	35 (26)	29 (29)	41 (22)	0.063	105 (27)
Chronic Kidney Disease, n (%)[c]	38 (38)	39 (39)	73 (40)	0.962	150 (39)
Chronic Obstructive Pulmonary Disease, n (%)	38 (38)	34 (34)	69 (38)	0.854	141 (37)
Coronary Artery Disease, n (%)	43 (43)	47 (47)	92 (51)	0.535	182 (48)
Hypertension, n (%)	83 (83)	89 (90)	162 (88)	0.310	334 (87)
Diabetes Mellitus, type 2, n (%)	42 (42)	37 (37)	60 (33)	0.280	139 (36)

[a]Fisher's exact test or analysis of variance

[b]Two participants in the upper albumin group were missing BMI

[c]Chronic Kidney Disease: established diagnosis based a three-month history of an estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m2 [23].

Table 2: Cox Proportional Hazard Model: Mortality following RC Discharge (n=381).

Discharge Variable	Hazard Ratio (95% CI)	P-value**
Albumin ≤3.0*	1.41 (1.04 - 1.92)	0.029
Albumin 3.1-3.3	1.20 (0.88 - 1.62)	0.247
Albumin ≥3.4	1	
Age ≥85	1.87 (1.33 - 2.63)	<0.001
Age 75-84	1.27 (0.93 - 1.73)	0.135
Age 65-74	1	
BMI <18.5	2.06 (1.13 - 3.75)	0.018
BMI 18.5-29.9	1.31 (0.94 - 1.81)	0.110
BMI ≥30	1	
CHF Diagnosis Yes	2.28 (1.74 - 2.99)	<0.001
CHF Diagnosis No	1	

*Note: Since the assumption for proportional hazards was rejected for Albumin. ≤3.0, the hazard ratio may be viewed as an average effect over time. The other variables in the model met the proportional hazards assumption.

** Compared to reference group.

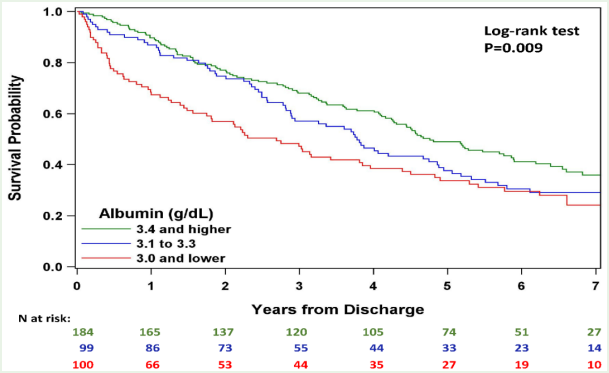

Figure 1: Kaplan-Meier Estimates of Survival according to Discharge Albumin.

times the hazard ratio was even smaller. In analyses investigating SA as a continuous variable (rather than transformed into three groups), there was a significant linear trend indicating that lower discharge SA was associated with higher mortality risk (p=0.010); this variable, too, had departures from proportional hazards.

Discussion

Studies of both community-dwelling and hospitalized older adults demonstrate a strong inverse association between SA and mortality. This association differs from what is demonstrated in the current study in terms of how long the discharge SA remains significantly associated with mortality risk. In the community-based studies, the incident SA remains significantly associated with mortality risk for up to 12 years [1-4]. In contrast, studies of patients discharged from an acute care hospital indicate this association remains significant for only 12 months [1,6-9]. The current study indicates that results for older adults discharged from a RCRU are intermediary between hospitalized and community-dwelling older adults; discharge SA remains significantly associated with mortality for two years. There are several possible reasons for these differences. Most community-residing healthy older adults have SA levels above 3.8 g/dL, at least untilthe age of 90 years [1,23]. Fewer than one percent of community-dwelling subjects have SA levels <3.5 g/dL and several studies of community-dwelling older adults used a low SA reference range of < 4.0 g/dL [1,4,23]. Consequently, none of these studies could assess the impact of very low SA (i.e., SA<3.0 g/dL) on mortality as so few of the subjects had SA in this range. Among community-dwelling older adults, the population variance in SA is relatively narrow and SA appears to be a relatively stable indicator of health status. Among hospitalized older adults, the prevalence of low and very low SA is high and SA appears to be more of a marker of acute mortality risk,

which is probably the reason why the relationship between discharge SA and mortality remains significant for only one year.

In the current study, 26 percent of the older adults discharged from the RCRU had a very low discharge SA ≤3.0 g/dL while 26 percent had a low discharge SA 3.1 to 3.3 g/dL. Compared to the subjects with a discharge SA ≥3.4 g/dL (normal albumin group), those with a very low SA were at significantly higher risk for subsequent mortality. In the current study, the difference between the middle(3.1 to 3.3 g/dL) and upper (≥ 3.4 g/dLwhich is at or above the reference value) groups did not reach statistical significance; the Kaplan-Meier estimates are very similar through year 2, but diverge subsequently when there are fewer participants at risk and thus lower power to detect meaningful differences. A larger study would better elucidate the relationship at later years. The relationship between SA and mortality in this middle SA group may be closer to that of community-dwelling older adults.

In the current study, the mean SA fell well below most community-dwelling and hospitalized studies causing concern for recuperative care older adults' future prognosis and health related outcomes. Similarly, an association between low discharge SA and mortality in older adults in rehabilitation settings that remained significant in the short-term (up to one-year post-discharge) has been shown in other studies [1,4,10,11].

Conclusions

In summary, the findings of this study indicate that among older adults discharged from a RCRU, a SA level ≤ 3.0 g/dL is associated with increased mortality out to two years compared to patients discharged with SA ≥3.4 g/dL; no association was found between SA and longer-term mortality. Low SA levels at discharge from a RCRU identify older patients at increased mortality risk suggesting they need more aggressive monitoring and care after discharge.

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