# ARE ALBUMIN LEVELS A GOOD PREDICTOR OF MORTALITY IN ELDERLY PATIENTS WITH NECK OF FEMUR FRACTURES?

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**ABSTRACT**

**Background**

Neck of femur (NOF) fractures are associated with significant morbidity and mortality in elderly people with multiple co-morbidities; making management of this patient subgroup challenging. Predictors of an increase in morbidity and mortality would therefore provide a useful framework for the assessment and management of this demographic. Within the current literature, hypoalbuminaemia (<35g/dl) has been highlighted as being a good biochemical predictor of short-term mortality (<12 months). Our aims were to assess whether there was an association between low albumin levels and short-term mortality and whether the severity adversely affects outcomes.

**Materials and Methods**

Patients admitted to our large district hospital between January 2011 and December 2012 who had sustained a NOF fracture, were over 65 years old and had a pre-operative albumin level were included. The study concluded in July 2014. Demographic and pre-operative function and albumin data was collated retrospectively. Correlation with mortality was made.

**Results**

471 patients had usable data. Mean pre-operative albumin level was 29.5g/dl (SD 6.22g/dl) in patients who died and 32.8g/dl (SD 6.43g/dl) in patients who survived during the study period. Pre-operative albumin level was significantly associated with survival (hazard ratio 0.957: 95% CI (0.937, 0.978); p<0.001) A reduction of 1g/dl in pre-operative albumin is associated with an increased hazard of death of 4.3%.

**Conclusions**

Early identification of patients with hypoalbuminaemia on admission with a venous blood sample and timely input from orthogeriatrians could optimise these patients pre- and post-operatively. This may enable rates of morbidity and mortality to fall. Hypoalbuminaemia may be a reasonable predictor of shorter-term mortality in

this patient subgroup. However, this may reflect existing co-morbidities rather than an isolated cause. This study supports a correlation between hypoalbuminaemia and poorer outcome for patients with NOF fractures.

**Keywords**

Hypoalbuminaemia, neck of femur, fracture, survival, trauma

## INTRODUCTION

Patients presenting with a fractured neck of femur are associated with significant morbidity and mortality.[1, 2] The National Hip Fracture database in England suggests that 8.2% of this patient group will die at or around 30 days and somewhere between 20-35% will not survive past 12 months.[3] However, with an ageing population it is predicted that the number of patients presenting with a neck of femur fracture will increase,[3, 4, 5] in spite of measures taken to address fracture prevention.[6] Identification of factors associated with survival, and estimation of survival of specific sub-groups differentiated by these factors, is therefore a useful health care tool to employ in order to help correct abnormalities and reduce healthcare costs.

Several systems and markers have been used to predict mortality. Many encompass established risk factors such as; age, sex, ASA [American Society of Anesthesiologists] grade and delay to surgery. The Nottingham Hip Fracture Score has been reliably shown to predict 30-day mortality,[6] although some factors may not be readily available in the acute situation. The POSSUM score (Physiological and Operative Severity Score for the enumeration of Morbidity and Mortality) was initially designed for use with general surgical conditions, but has been adapted for orthopaedic use.[7, 8] It has shown to perhaps overestimate mortality.[9] These scoring systems are often not the most convenient to complete in an acute clinical setting.

Biochemical markers have also been utilised.[10] Lactate is widely used in the trauma and sepsis setting to look at adverse outcomes and has been shown to be a predictor in patients with hip fractures.[11] End Tidal $CO_2$ has been postulated, mainly looking for evidence for metabolic acidosis in the pre-hospital setting. This has been found to be consistent predictor for mortality.[12] Albumin has often been used in conjunction with total lymphocyte count to give an indication of protein energy malnutrition.[13, 14] Few studies look at albumin as an isolated marker.[15, 16]

Low albumin levels (less than 35 g/dl) are associated with poor nutritional states;[17] chronic illness, for example: liver and renal dysfunction and concurrent infection.[18] If low levels of albumin are not addressed, complications may occur, including decubitus ulcers, poor wound healing and infection secondary to leg oedema, therefore

potentially prolonging length of hospital stay.[18, 19, 20] Low albumin levels in a general elderly hospitalised population have been shown to be present in patients that have died. Hypoalbuminaeamia in this group has been demonstrated as a statistically significant risk factor for mortality.[21, 22, 23] In patients with decreasing physical activity level and lower albumin levels, mortality rates can increase up to three times.[24]

The level of serum albumin can be determined simply by performing a bedside blood test. There is no universal classification for the degree of hypoalbuminaemia.

Our aims were to assess whether there was an association between low albumin levels and patient survival in patients with neck of femur fractures; whether the severity of low albumin adversely affects outcome and whether highlighting these patients would be a useful prognostic tool.

## MATERIALS AND METHODS

Data was obtained retrospectively from our district hospital hip fracture database and clinical results server between January 2011 and December 2012. This was followed up until the date of curtailment of the study on 31st July 2014. These databases were cross-examined to ensure that no patient was missed from data collection. The mortality data is recorded on both databases and therefore able to be verified. These systems are linked to the community systems and therefore outpatient mortality is recorded and updated accordingly. Patients were included if they had sustained a fractured neck of femur, were over the age of 65 and had a serum albumin level pre-operatively.

The following data was obtained from each patient: gender; age (years) at fracture; time to surgery (hours); albumin level on admission (g/dl); ASA grade; length of stay in hospital (days); pre-operative ambulation status; survival status (i.e. alive or dead) at the curtailment of the study. The time variable for the study was survival from the date of the procedure; for patients who died by the date of study curtailment of 31st July 2014 the time to death (days) was recorded. Patients who were not recorded as having died by 31st July 2014 were recorded as right-

censored observations, with an associated time calculated as the number of days from surgery until the date of study curtailment. Pre-operative ambulation status was categorised as *good* (requires 0 or 1 walking aids); or *poor* (requires 2 or more walking aids or frame; or is wheelchair- or bed-bound).

Missing data was examined for suitability for imputation, and imputed using expectation maximisation where appropriate.

For the purposes of graphical comparative analyses, patients with albumin levels of 35 g/dl or above were initially categorised as *Normal*; patients with albumin levels of 25-34 g/dl were classified as having mild hypoalbuminaemia ("*mild*"); patients with albumin levels of 15-24 g/dl as having moderate hypoalbuminaemia ("*moderate*"); and patients with albumin levels of 15 g/dl or less as having severe hypoalbuminaemia ("*severe*"). However, due to very low frequencies of patients in the *severe* category, this category was subsequently combined with the *moderate* category.

Parametric survival analysis was conducted on the patients, to determine the effect of albumin level on survival, controlling for other factors and covariates as recorded above, following exploratory checking for co-linearity between candidate predictor variables. A number of candidate survival distributions were considered; including the exponential, Gompertz, Weibull, log-normal and log-logistic distributions. An appropriate distribution was selected by assessment of the Akaike Information Criteria (AIC) statistic for null models under each of the above distributions. Distributions which could be parameterised in either the proportional hazards or accelerated failure time metric (including the exponential and Weibull distributions) were considered in both alternative forms, with the assumption of proportional hazards tested where appropriate. Residuals were inspected post-estimation to assess the fit of the chosen model.

All statistical analysis was undertaken using Stata/IC Version 11.1.

## RESULTS

Data was initially obtained from 496 patients. Twenty-five patients were excluded on the grounds of no operation performed; leaving a data set of 471 usable patients: 142 males (30.2%) and 329 females (69.8%). The sample is summarised descriptively in Table 1.

Five patients had missing values relating to ASA score. These values were imputed using expectation maximisation.

The mean pre-operative albumin level amongst patients who had died during the study period was 29.5 g/dl (SD 6.22 g/dl). The mean pre-operative albumin level amongst patients who did not die during the study period was 32.8 g/dl (SD 6.43 g/dl). Amongst the 152 patients whose pre-operative albumin level was categorised as *normal*, 51 patients (33.6% of this sub-group) died during the course of the study. Amongst the 240 patients whose pre-operative albumin level was categorised as *mild*, 134 patients (55.8% of this sub-group) died during the course of the study. Amongst the 79 patients whose pre-operative albumin level was categorised as *moderate/severe*, 54 patients (68.4% of this sub-group) died during the course of the study.

Exploratory procedures did not reveal evidence for co-linearity between any of the candidate variables. The AIC statistics associated with the Weibull, log-logistic and log-normal distribution were very similar (1488 – 1494 for null models); whereas the AIC statistics of the exponential and Gompertz models indicated these distributions to be less good fits to the data (1614 and 1521 for null models respectively). However, the log-cumulative hazard plot (Figure 1) indicated that the proportionality of hazards assumption across the three levels of the albumin variable was tenable. Hence the Weibull distribution, parameterised in the proportional hazards metric, was selected to describe the data.

A survival analysis with all variables entered using forced entry found pre-operative albumin level to be significantly associated with survival (hazard ratio (HR) 0.957: 95% confidence interval for HR: (0.937, 0.978); p<0.001). Hence each reduction of 1 g/dl in pre-operative albumin is associated with an increased hazard of death of 4.3% at best estimate, and controlling for other variables. A 10 g/dl reduction in pre-operative albumin is associated with an increased hazard of death of 52.4%. Inspection of Cox-Snell residuals did not reveal any evidence for violation of modelling assumptions.

Amongst the controlling variables, gender, age at fracture and ASA score were also significantly associated with raised hazards, with greater hazard of death being found in males, in older patients and patients with higher ASA scores. At best estimate, and controlling for other variables, the hazard of death in males is 30% higher than in females; each year of advancing age is associated with an increased hazard of 2.0%; and each additional point recorded on the ASA scale is associated with an approximate doubling of hazard of death.

Ambulation status, time to operation and length of hospital stay were not significantly or substantively associated with a raised hazard of death. The model chi-squared statistic of 97.5 for this model follows a chi-squared distribution with 7 degrees of freedom and is statistically significant ($p$<0.001), indicating that parameter estimates as a group are significantly different from zero. Hazard ratios (HRs), associated 95% confidence intervals (CIs) and p-values for all factors and covariates considered in the analysis are summarised in Table 2 below.

Survival experience of patients grouped by pre-operative albumin levels (categorised as *normal*, *mild* or *moderate/severe* as defined above) is illustrated in Figure 2 below.

Comparison of patient characteristics revealed few substantive differences between those patients for whom albumin was recorded (496; 51.9% of all available patient records) and those patients for whom albumin was not recorded (460; 48.1% of all available patient records). The mean age of patients for whom albumin levels were recorded was 82.1 years, the mean age of patients for whom albumin levels were not recorded was 80.6 years. Gender balance was quite similar across the two groups: 70% of patients for whom albumin was recorded were female; 76% of patients for whom albumin was not recorded were female. ASA scores were also broadly similar across the two groups, with about half of patients in both groups having a score of 3. Such similarities across the

groups suggest that exclusion of patients from the analysis for whom albumin levels were not recorded is not introducing any systematic bias to the sample.

For the entire sample, estimated median survival time is 929 days, with a 95% confidence interval for median survival (days) given by (644, 1143). Amongst sub-groups categorised by pre-operative albumin levels, median survival time is about 300 days for patients with pre-operative moderate/severe hypoalbuminaemia; about 750 days for patients with pre-operative mild hypoalbuminaemia; and in excess of 1200 days for patients with normal levels of albumin pre-operatively. In all patients, a rapid early reduction in survival is experienced, followed by a levelling off beyond about 600 days.

## DISCUSSION

In this current study we have demonstrated that pre-operative serum albumin levels in patients presenting with neck of femur fractures is a statistically significant predictor of mortality. This compares well with previously published literature. Within the general elderly population who is hospitalised, mortality rates have been quoted as 8.4% to 16.4%.[21, 22] Silva *et al*. reported higher rates of hospital mortality in the general elderly population are associated with lower levels of serum albumin. They report a mortality rate of 28.9% in patients presenting with hypoalbuminaemia.[21] In addition, studies have also demonstrated a correlation between mortality at one year following discharge and albumin levels lower than 35g/dl at admission.[23] Our data confirms this finding.

With regard to neck of femur fracture management, Pimlott *et al.* published similar findings and demonstrated a statistically significant association between low albumin levels and mortality. Short-term mortality was 2.5 times more likely in patients with hypoalbuminaemia.[16] Our study shows that the lower the level of albumin, the increased risk of poor outcome. Substantial drops in albumin levels, that is by 10g/dl increase the risk of death by over 50%. Recently, Kieffer *et al.* demonstrated that albumin alone could accurately predict mortality at one year,[15] which our findings can support.

Unlike the study by Kumar *et al.* we did not find that time to surgery was a significant factor.[25] However, our mean time to surgery was less than 36 hours, which is in keeping with nationally agreed targets.[26] Other factors that were statistically significant were gender, age and ASA grade.

O'Daly *et al.* suggested that serum albumin in addition to total lymphocyte count may act as markers of malnutrition; this being linked to protein energy malnutrition. The authors suggested that these markers maybe predictors of adverse outcomes in patients with neck of femur fractures.[13] However, in their study only serum albumin level upon admission and age were found to be independent prognostic factors for mortality at 12 months. Koval *et al.* found that patients with a combined low total lymphocyte count and serum albumin at admission were 3.5 times more likely to die within 12 months of operative management.[14] From our study, we have shown that albumin levels alone, as a single bedside test may be a single predictor of mortality. Other scoring systems may be difficult to complete in busy trauma units, where hospitals strive to meet national operative targets and information may not always be available or achievable prior to surgery concerning pre-fracture status.

Serum albumin levels are not the only determinant with regard to managing patients with neck of femur fractures. We recognise that our study has limitations. This patient subgroup often has multiple co-morbidities that are likely to be factors in patient survivorship. We have looked at albumin levels in isolation and other co-morbidities may confound the results. Our study has highlighted that addressing albumin levels might be offer better survivorship in an already frail patient group. Lower albumin levels do increase the risk of poorer outcomes from other co-morbidities; they are associated with loss of muscle mass from the appendicular skeleton. Muscle functioning may be interrupted due to the nature of the surgery for hip fractures. Subsequent reduced mobility may ensue and thus, putting patients at further risk of post-operative complications.[18]

We also recognise that although 956 patients presented with a neck of femur fracture to our unit within the study period, only 471 had useable data. This was due to the fact it is not presently routine practice to perform a serum albumin pre-operatively. This may be a source of bias and prospective data may have addressed this. However, separate analysis has not demonstrated any significant difference between the groups. Many patients did have an

albumin level within their post-operative period; however, this may have confounded results, as the level of albumin may have been affected secondary to the patient's surgery.

We recommend that albumin levels should be measured pre-operatively in order to direct our limited orthogeriatric and dietetic services. We recognise that nutritional supplementation may not reduce mortality but may reduce overall complications.[19] Measurement of albumin levels has not changed our operative decision-making and patients still receive recommended operative management as per national guidelines.[26] We have now recognised the pre- and post-operative optimisation of the patient should include addressing serum albumin levels.

## CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

## ETHICAL APPROVAL

For this type of study formal consent is not required.

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