Does Serum Albumin Level Affect the Healing Outcomes of Simple Diaphyseal Tibial Fractures?

Sabir Ali, Ajai Singh, Abbas A. Mahdi[1], Rajeshwar N. Srivastava, Kumar Shantanu
Departments of Orthopaedic Surgery and [1]Biochemistry, King George's Medical University, Lucknow, Uttar Pradesh, India

Correspondence: Dr. Ajai Singh, Department of Orthopaedic Surgery, King George's Medical University, Lucknow - 226 018, Uttar Pradesh, India. E-mail: as29762@gmail.com

ABSTRACT

Aims: To quantify the serum albumin level and its correlation with fracture healing progression and outcomes in adult patients.

Settings and Design: A prospective cohort study at an institutional trauma center.

Materials and Methods: A total of 50 adult patients with simple, fresh traumatic diaphyseal fractures of both bones of the leg managed conservatively were included in the study. Serum albumin was measured initially and at the 6th week postfracture. The clinico-radiological follow-up was done to analyze the fracture healing progression and their final outcomes, which were correlated with the quantified serum albumin level of the patients.

Statistical Analysis Used: Student *t*-test, Mann–Whitney U-test and Pearson correlation coefficient.

Results: As per the last clinico-radiological follow-up at the 24th week, patients were grouped into two groups: Group I (normal union $n = 38$) and Group II (impaired healing $n = 12$). The mean serum albumin levels were significantly higher in Group I when compared to Group II. The association between the serum albumin level at baseline and at the 6th week was moderate. The best cut-off measure of serum albumin level was 3.45 g/dL, both at baseline and at the 6th week after fracture to predict the healing outcome. The correlation of serum albumin levels with fracture healing outcomes was statistically significant.

Conclusion: Serum albumin is moderately associated with the baseline and 6th-week values and showed a positive correlation with the bony healing progression and may provide an early predictor of the healing outcomes of simple diaphyseal tibial fractures.

Key words: Diaphyseal fractures, fracture healing outcomes, serum albumin

ملخص البحث :

هدفت هذه الدراسة المستقبلية لتحديد مستوى بروتين الألبومين في الدم وعلاقته مع شفاء الكسور لدى المرضى البالغين. تضمنت الدراسة 50 مريضاً بالغاً مصاباً بكسور بسيطة في عظمتي الساق وتمت المتابعة السريرية والشعاعية لتقييم الشفاء وعلاقته بمستوى بروتين الألبومين في الدم. قسم المرضى إلى مجموعتين وكانت مستويات الألبومين أعلى في المجموعة الأولى مقارنة مع المجموعة الثانية. وكان لارتباط مستويات الألبومين مع نتائج التئام الكسور دلالة إحصائية وقد يستخدم هذا الارتباط كمؤشر مبكر لالتئام كسور الساق.

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INTRODUCTION

The subcutaneous position of the tibial bone leads to a greater incidence of fractures due to less soft-tissue coverage, and consequently, there is a higher incidence of impaired healing.[1-5] Diaphyseal tibial non-unions are estimated to occur in 2-10% of all tibial fractures.[6,7] Fracture impairment (delay or nonunions) causes prolonged disability of the patient with substantial pain that puts an extra burden on the patient and presents challenges to the treating surgeon.[8,9] Many risk factors are associated with these fractures such as extensive soft tissue damage, gap at the fracture site, open fractures, poor mechanical stability, nutritional factors and administration of pharmacological agents such as nonsteroidal antiinflammatories, smoking, etc.[10-15] However, till now nutritional factor are not considered to use as a prognostic biomarker in parallel to clinic-radiological diagnosis for the prognosis of non-union early. Human serum albumin (69 kDa) is a multifunctional, nonglycosylated, and negatively charged plasma protein, which is used as a marker to measure the nutritional health of an individual.[16] An albumin level of 3.5 g/dl or higher is widely accepted as normal.[17] However, some studies have indicated that a low albumin level is an indicator of malnutrition, particularly in orthopedic trauma patients.[17,18] In many studies, it has been found that protein depletion leads to increase in mortality, morbidity, wound infection, surgical failure, sepsis, as well as an impaired fracture union.[12-15,19] A study by Koval *et al*.[20] demonstrated that an albumin level of <3.5 g/dl was an early predictor of a delay in fracture healing, increased hospital stay as, well as a high mortality rate.

Miklos *et al*. demonstrated the ability of serum albumin to induce mesenchymal stem cell growth on the surface of bone allografts.[16] As the proliferation of bone-forming cells is the rate-limiting factor in graft remodeling, the simple serum albumin coating of bone grafts may be enough to improve graft integration in a compromised bone-healing model.[17]

Yamaguchi *et al*., reported the femoral-diaphyseal fractures of rats and determined that fracture healing induces an increased production of albumin, a major protein component produced from femoral-diaphyseal tissues, which has an anabolic effect on bone components.[18]

Diaphyseal tibial fractures are common and their increased risk of impaired healing increases the burden on both the patient and surgeon.[8,9] Out of the many factors previously mentioned, nutritional status of the patient was positively correlated with fracture healing, in which it was shown that serum albumin level has a major impact on bone regeneration.[10-15] Based on above findings and wide availability of cost effective serum albumin test, we studied the correlation of tibial fracture healing outcomes with serum albumin level based on the hypothesis that fracture healing outcomes of simple diaphyseal tibial fractures are associated with serum albumin level.

MATERIALS AND METHODS

This is a prospective cohort study carried out between 2011 and 2013 at our institutional trauma center. A total of 61 patients, aged between 18 and 45 years, who had presented with simple, fresh (<7 days) traumatic diaphyseal fractures (42-A1, A2 and A3, as per as AO muller classification) of both bones of the leg with an abnormal albumin level, but having normal ferritin and total lymphocyte count were included in the study. Exclusion criteria included age of <18 and >45 years; osteoporotic fractures; polytrauma; pathological fractures; compound or infected fractures; alcoholic; smoker; immune-compromised; intact fibula; uncontrolled diabetes; bile duct obstruction; chronic inflammatory bowel disease; malnourished; and prolonged use of anabolic steroids, thiazides, diuretics, hormonal therapy, nonsteroidal antiinflammatories, calcium, fluorides, and immunosuppressive drugs. The enrolled patients were managed conservatively by reduction setting and above knee plaster applied under local or general anesthesia and were discharged after 24-48 h with the standard advice written on a discharge card. Peripheral blood (2 ml) was collected under standard aseptic technique at the time of management and at the 6th week for quantification of the serum albumin level using the ELITech clinical system. The serum albumin quantification was performed in duplicate as per as their protocol. To measure the progression of fracture healing, clinico-radiological follow-up was done on the 6th, 10th, 16th, 20th, and 24th week postfracture.

Clinical examination of the fracture site includes the assessment of abnormal mobility (if required), bony tenderness, and transmitted movements. The clinical sign of bony union was defined as the stage in the healing when the fracture site has no tenderness, no abnormal mobility with no evidence of transmitted movements. The radiological examinations were done using radiographic union scale for tibial (RUST) scoring system by taking standard plain radiographs of the full length of the leg in anteroposterior (AP) and lateral views. The radiographic scoring was done by the two orthopedic surgeons separately and blindly, and the average of the two scores was given to each radiograph.

At the last radiological evaluation, that is, the 24th week postfracture, the patients were divided into two groups. Group I comprised those with normal healing with a RUST score ≥7 and Group II comprised those patients with impaired healing with a RUST score <7 [Figure 1]. The radiographic sign of bone healing was defined when bony callus was evident on at least 3 cortices in standard AP and lateral views and with a RUST score greater or equal to seven.[13]

Fracture healing progression and their outcomes by RUST scoring were further correlated with the quantified serum albumin level of these patients. Also, a definite cut-off level of serum albumin level was identified using ROC curve as an early predictor of fracture outcome.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows program (15.0 version). The continuous variables were evaluated by mean (±standard deviation) or range value when required. For comparison of the means between the two groups, analysis by Student's *t*-test with 95% confidence interval, Mann–Whitney U-test, and Pearson correlation coefficient was used. A $P < 0.05$ or 0.001 was regarded as significant.

RESULTS

A total of 61 patients were enrolled in our study, in which 50 patients were studied with 11 patients lost to follow-up. According to the last clinico-radiological follow-up, that is, at the 24th week postfracture, these patients were divided into two groups: Group I ($n = 38$) with normal bony union and Group II ($n = 12$) with impaired bony union. The mean time of healing in Group I patients was 18.3 ± 3.1 weeks. Table 1 describes the baseline characteristics of the patients in Group I and Group II, which do not show a statistically significant difference ($P > 0.05$) with the exception of the mean albumin level. The mean serum albumin levels were significantly ($P = 0.045$) higher in Group I when compared to Group II [Table 1]. The mean serum albumin levels between the baseline and at the 6th week postfracture were 3.54 ± 0.23 and 3.66 ± 0.29 g/dL, respectively, reflecting a change of 0.12 ± 0.26 g/dL. The association between baseline albumin levels and albumin levels at the 6th week was of moderate level ($t = 3.161$; $r = 0.513$; $P < 0.001$).

However, receiver-operator curve analysis was performed to determine an appropriate cut-off albumin level (baseline and 6th week) to predict the healing outcome. Albumin at the baseline, area under the curve was 0.689, which indicated an average efficacy of the criteria and the cut-off >3.45 was predicted to be 71.1% sensitive and 58.3% specific [Figure 1]. At the cut-off of albumin level at the 6th week, the area under the curve was 0.865, which indicated an excellent predictive ability of the marker. At cut-off >3.45, the criteria were regressed to be 92.1% sensitive and 66.7% specific [Figure 2].

The majority of Group I cases ($n = 27$; 71.1%) had a baseline albumin level of >3.45, while the majority of

Table 1: Comparison of baseline characteristics of two groups

Characteristic	Group I union ($n = 38$) (%)	Group II impaired union ($n = 12$) (%)	Significance of difference
Mean age±SD (range) in years	34.37±9.21 (19-48)	35.92±4.94 (30-44)	$t=0.555$; $P=0.581$
Gender			
Male	34 (89.5)	8 (66.7)	$P=0.082$ (Fisher exact test)
Female	4 (10.5)	4 (33.3)	
Site			
Left	22 (57.9)	5 (41.7)	$\chi^2=0.967$; $P=0.325$
Right	16 (42.1)	7 (58.3)	
Mode of injury			
Fall from height	11 (28.9)	1 (8.3)	$\chi^2=7.283$; $P=0.063$
RTA	22 (57.9)	10 (83.3)	
Simple fall	5 (13.2)	0 (0)	
Slip	0 (0)	1 (8.3)	
AO type			
A1	9 (23.7)	6 (50.0)	$\chi^2=3.216$; $P=0.200$
A2	16 (42.1)	4 (33.3)	
A3	13 (34.2)	2 (16.7)	
Mean Hb±SD (range) g/dl	10.33±1.35 (8.4-12.9)	10.15±1.22 (8.4-12.3)	$t=0.409$; $P=0.684$
Mean albumin level±SD (range)	3.58±0.21 (3.1-3.9)	3.43±0.25 (3.0-3.9)	$t=2.056$; $P=0.045$

SD – Standard deviation; RTA – Road traffic accident; Hb – Hemoglobin
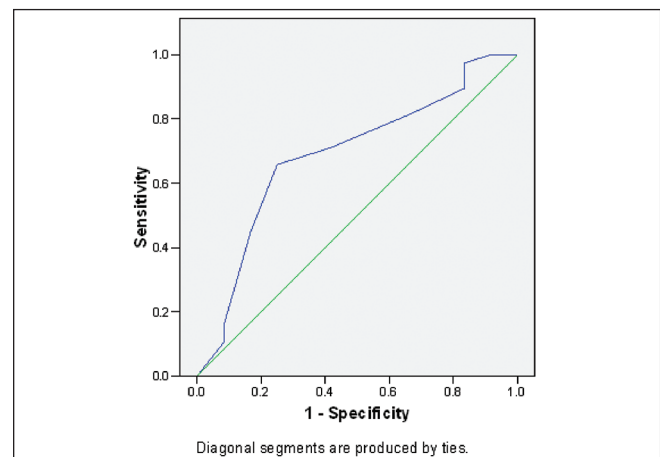
Figure 1: Receiver-operator curve analysis to find out an appropriate cut-off albumin level at baseline to predict healing as an outcome

Group II cases (n = 7; 58.3%) had albumin level <3.45 (χ^2 = 3.418; P = 0.064). However, this association was not statistically significant (P = 0.064). Although the majority of Group I cases (n = 35; 92.1%) had 6th week albumin levels of >3.45, the majority of Group II cases (n = 8; 66.7%) had albumin levels of <3.45 and their association was statistically significant (χ^2 = 18.34; P < 0.001).

The group with high serum albumin levels at the baseline and at 6th week showed significantly high RUST score as compared to the low albumin cut-off group. At each of the follow-up intervals, the difference in outcome RUST scores of the two albumin category groups was significant [Figures 3 and 4]. A mild to moderate correlation between baseline albumin levels and fracture outcome analyzed using RUST score was observed, which was also statistically significant. Also, a statistically significant difference in mean albumin levels at the 6th week was observed between the two groups (t = 4.725; P < 0.001).

DISCUSSION

Diaphyseal tibial fractures are common and lead to a substantial burden on patients, the surgeon, and the healthcare system due to healing impairment.[8,9] Many factors are responsible for healing impairment,[10,11] including the nutritional status of the patient in which the level of serum albumin has a major impact on bone regeneration.[10,11,12-15] Therefore, this study correlated the simple diaphyseal tibial fracture healing outcomes with serum albumin level, due to the hypothesis that fracture healing outcomes of simple diaphyseal tibial fractures are associated with serum albumin level.

Among a plethora of various types of biochemical markers, serum albumin remains the choice in assessing malnutrition[21] To the best of our knowledge, there are no reports on the relationship between serum albumin and tibial fracture healing. However, as serum albumin is commonly used as a marker for malnutrition, in this section we have discussed some of the malnutrition-based studies, in which albumin is used as one of the main parameters. Dwyer *et al*.[15] was the first to study the association of nutritional status with fracture healing of the tibial in humans and found an insignificant association. Similarly, Ali *et al*. also found a statistically insignificant association of fracture healing outcomes with the nutritional status of patients, however in the same study, they also found that the serum albumin level is associated with healing outcomes.[22] However, some studies in animal models, that is, Day and DeHeer,
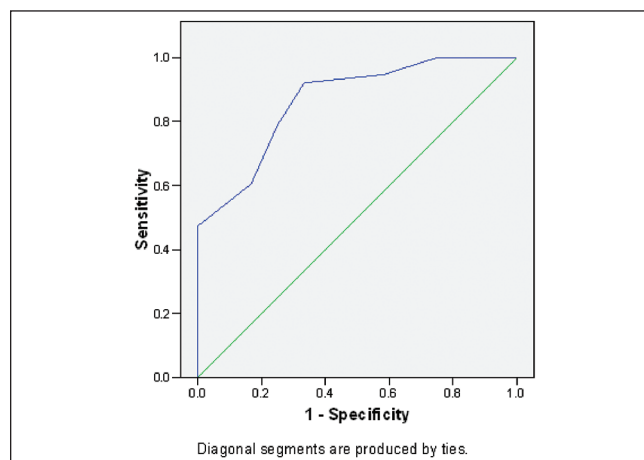
Figure 2: Receiver-operator curve analysis to find out an appropriate cut-off albumin level at 6 weeks to predict healing as an outcome
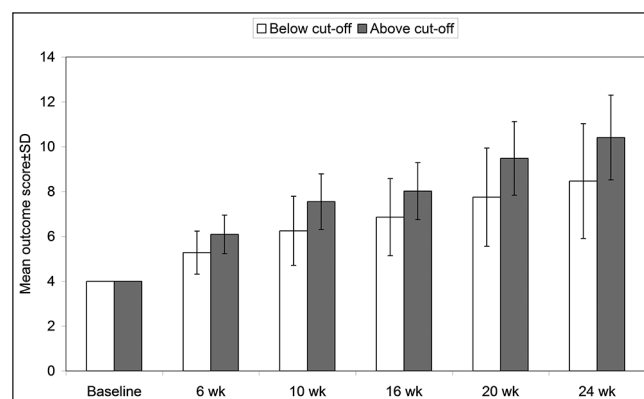
Figure 3: Association between baseline albumin levels and healing outcome at different levels
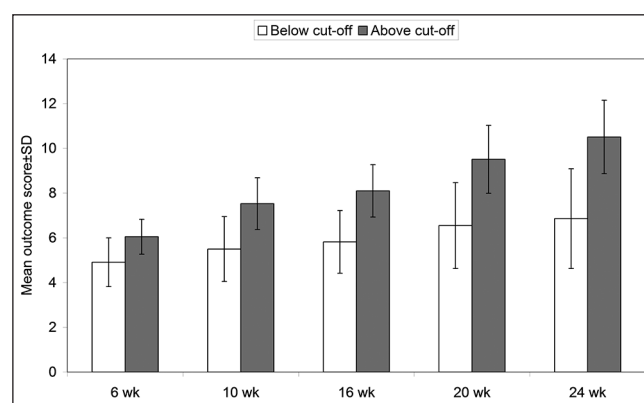
Figure 4: Association between albumin levels at 6 weeks and healing outcome at different levels

Einhorn *et al*., and Guarniero *et al*.[13,14,23] found that tibial fracture healing is significantly associated with nutritional status. Many studies correlate malnutrition with increased mortality and morbidity, surgical failure, wound infection, sepsis, impaired fracture union, and wound healing.[12-15,19] Koval *et al*. also demonstrated that an albumin level

of <3.5 g/dl was a predictor of delay in fracture healing, long hospital stay, as well as a high mortality rate.[20]

The present study has been conducted on humans to correlate serum albumin level with simple diaphyseal tibial fractures. Applying the receiver-operator curve analysis, we found the cut-off >3.45 for both albumin at baseline and at the 6th week. In this study, we have concluded that serum albumin is moderately associated (r = 0.513; P < 0.001) with the baseline and 6th week value and shows a positive correlation with the bony healing progression, which may predict the healing outcomes of simple diaphyseal tibial fractures. We also identified that the correlation of albumin at the 6th week was an excellent predictor of healing outcome (92.1% sensitive and 66.7% specific) than the albumin level at the baseline. Furthermore, the association of albumin with fracture outcomes was found to be statistically significant.

In summary, our results reinforce findings that serum albumin level is correlated with tibial fracture healing and may affect the final outcome of healing.[13,14,22,23] Also, we recommend early interference in those patients that have a low albumin level through intravenous infusion of albumin supplements or early (primary) bone graft, so that the healing process will be properly achieved within the optimal time frame.

CONCLUSION

Presently, clinicians are unable to conclusively identify fracture impairment early, that is, delayed and nonunions. However, in our study, we have concluded that serum albumin may be a predictor of the healing progression of diaphyseal tibia and healing outcomes. We suggest that further studies be conducted with larger patient groups.

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Conflicts of interest
There are no conflicts of interest.

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