MMed in Orthopaedic Surgery
For candidate Dane Maimin

Hypoalbuminaemia in orthopaedic trauma patients in a rural hospital in South Africa

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Format

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Hypoalbuminaemia in orthopaedic trauma patients in a rural hospital in South Africa

Introduction

Trauma is one of the leading causes of morbidity and mortality in our world today. In 2013 it was estimated that 973 million people sustained injuries that required medical care and 4.8 million people died from their injuries. (1) Over 90% of trauma related deaths occur in low- and middle- income countries. In South Africa trauma related mortality is six times higher than the global average and 50000 trauma related deaths were recorded in 2009 alone. (2,3) For every death that occurs it is estimated that there are between 10 and 50 injured survivors, half of whom will have a permanent disability. (4)

Trauma results in a variety of physiological changes known as the acute phase response. (5) Albumin is a negative acute phase reactant and serum albumin levels typically decrease following trauma. Hypoalbuminaemia is a serum albumin of less than 35g/L. (6) While there is no specific gender predilection, the prevalence increases with age. (6) Extensive evidence shows that hypoalbuminaemia is a risk factor for peri-operative morbidity and mortality in elective and emergency surgery in orthopaedic surgery and other surgical disciplines. (7–17) Serum albumin levels taken on admission are used to identify patients at risk for mortality or morbidity related to surgical site infection, wound dehiscence, prolonged hospital stay, fracture non-union as well as decubitus ulcers, ARDS, thromboembolism, pneumonia and urinary tract infections. (7,10,12,14)

While the risks associated with hypoalbuminaemia is well established, data relating to the prevalence of hypoalbuminaemia in orthopaedic surgery trauma patients, especially in low- and middle-income countries (LMIC) remains limited. Most of the research has been done in high income settings. Studies have reviewed rates of hypoalbuminaemia in certain high-risk subgroups e.g., geriatrics, arthroplasty, and spines, however there is paucity of data regarding hypoalbuminaemia in orthopaedic surgery trauma patients in general. (7,10,12,13). A level one trauma centre in Germany reviewed 249 patients undergoing intramedullary nailing for diaphyseal femur fractures and found 39.4% of patients had a

serum albumin below 35g/L. (18) We are aware of only one paper that reported hypoalbuminaemia in orthopaedic trauma in an African setting, however the sample size in this series was relatively small, only closed femur fractures were included and it did not look at how HIV infection related to serum albumin. (9)

This study aims to investigate the prevalence of hypoalbuminaemia in orthopaedic trauma patients in a rural community in South Africa, where HIV/AIDS is highly prevalent. (19) Secondarily, we aimed to identify factors associated with an increased risk of hypoalbuminaemia.

Methods

A retrospective cross-sectional study was performed of data collected prospectively over a six-month period, from November 2018 to May 2019. Data was collected at Madadeni Hospital in Madadeni, KwaZulu-Natal, South Africa. Madadeni Hospital primarily services informal settlements surrounded by agricultural land. Many homes here do not have electricity or running water. The drainage population of Madadeni Hospital is approximately 900 000 people. (20) Patients presenting to Madadeni Hospital for the first time with orthopaedic injuries that required admission were assessed for eligibility for inclusion in the study. These injuries included fractures and dislocations involving the extremities and axial skeleton as well as muscle, ligament, and tendon injuries. Patients under the age of 13 years, those being readmitted, those with concurrent sepsis and cases of suspected or confirmed malignancy (i.e., pathological fractures) were excluded.

Demographic data and comorbidities were collected. The blood work used for the data analysis was collected on admission. Serum albumin level as well as haemoglobin were analysed. Normal albumin was defined as albumin between 35 - 50g/L. (6) HIV infection was viewed as an independent variable and use of antiretroviral treatment at the time of injury was noted. Data on the nature of the trauma, including polytrauma, multiple orthopaedic injuries or open injuries were collected. Polytrauma was defined as injuries sustained to more than one body region or organ system of which at least one is life threatening. Multiple orthopaedic injuries were defined as the presence of at least two orthopaedic injuries, each requiring a different method of treatment.

Statistical analysis was performed using Stata 15.0 (StataCorp. College Station, Texas). Continuous variables were reported as mean (± SD) or median (with interquartile range) and categorical variables as number and percentages, unless otherwise stated. The Shapiro-Wilk test was used to analyse the distribution of data. Differences in continuous variables were compared with the use of the unpaired t-test or the Mann-Whitney test (depending on the distribution of the data). Categorical data was compared using the Fisher's exact test (if any cell count was below 5) or the Chi-squared test (if no cell count below 5). The correlation between age and albumin level was assessed using Spearman's rank correlation test. Logistic regression was then employed to estimate the strength of association of categorical variables and hypoalbuminaemia. All tests were two-sided, and the level of significance was set at $p < 0.05$.

Results

In total, 330 patients met the criteria for inclusion in the study. Thirty-five patients were excluded due to problems with the blood sampling, leaving a final sample size of 295. Patient demographics and injury characteristics are summarized in tables 1 and 2. Most patients in the study were male (n=177; 60%). Ages ranged from 13 to 94 with the mean age being 42.5 years (95% Confidence Interval [CI] 40.4 - 44.6). Most patients had sustained isolated injuries, with 25 (8%) patients presenting with multiple orthopaedic injuries. Forty-two (14%) patients met the criteria for polytrauma, 101 (34%) injuries were classified as open, and five (1%) patients were injured because of gunshots. Ankle fractures were the most common injury with 32 (11%) patients, followed by 28 (9%) fractures of the hand (carpus, metacarpals, or phalanxes), 26 (9%) tibial shaft, 25 (8%) femur neck and 23 (8%) femur shaft fractures respectively [Table 2].

Of the 295 patients in the study, 265 (90%) were either aware of their HIV status on admission or were tested on admission. Thirty patients (10%) were unaware of their status and declined testing. Seventy-two patients (24.4%) were HIV positive. Sixty-six (92%) of these patients were already on antiretroviral (ARV) treatment when admitted. The remaining six who were not on treatment were newly diagnosed during the admission.

Forty-four patients (15%) had comorbidities other than HIV infection at time of admission, including 40 (14%) with hypertension, 14 (5%) with diabetes mellitus, 15 (5%) with previous pulmonary tuberculosis, three (1%) with chronic kidney disease, and four (1%) with COPD. Twenty (28%) of the HIV positive patients had other comorbidities, while 44 (20%) of the HIV negative or HIV untested patients had multiple comorbidities (including hypertension).

The mean albumin of the cohort was 37 g/L (SD 5.6; 95% CI 36.3 – 37.4), while the mean haemoglobin was 12.8 g/dL (95% CI 12.6 – 13.0). The albumin level decreased with age (Spearman rho -0.37, $p < 0.001$) and more than half (27/50) of patients 65 years or older were hypoalbuminaemic ($p < 0.001$). Female patients tended to have a lower albumin level, with a mean of 35.2 g/L compared to 38.2 g/L in men ($p<0.001$). Overall, 29% of the cohort was found to have hypoalbuminaemia. Approximately 60% of patients with femur neck fractures, 57% of cases of intertrochanteric fractures and 53% of tibial plateau fractures were diagnosed with hypoalbuminaemia at time of presentation. Femur neck fractures ($p<0.001$), intertrochanteric fractures ($p=0.004$), tibial plateau fractures ($p = 0.034$) and polytrauma ($p = 0.013$) was associated with hypoalbuminaemia.

The mean albumin level was lower in HIV positive patients when compared to HIV negative patients (35 .7 g/L vs 37.5 g/L, $p = 0.007$). HIV infection, per se, was however not associated with the presence of hypoalbuminaemia (Odds ratio [OR] 1.7; 95% CI 0.97-3.05; $p = 0.066$). Notably, HIV infection combined with another comorbidity (other than hypertension) was associated with a low serum albumin ($p = 0.02$). The presence of certain comorbidities other than HIV, like Diabetes Mellitus ($p = 0.001$), previous pulmonary tuberculosis ($p = 0.034$) and chronic renal failure ($p = 0.007$) was associated with hypoalbuminaemia. The presence of multiple comorbidities ($p < 0.001$) was also significantly associated with hypoalbuminaemia [Table 3]. Bivariate logistic regression revealed that patients ≥ 65 years of age had a 3.7 times higher risk for the presence of low serum albumin at time of presentation (95% CI 1.97-6.93). In a multivariate regression model patient age, tibial plateau fractures, polytrauma and the presence of a comorbidity other than hypertension remained significant predictors of hypoalbuminaemia ($p<0.001$) [Table 4].

Discussion

We reviewed the serum albumin levels on a variety of orthopaedic trauma patients admitted to a regional hospital in rural South Africa. The aim was to assess the prevalence of hypoalbuminaemia and to identify any potential groups at increased risk based on demographics, premorbid state, and nature of trauma. We found that 29% of patients included in this cohort had low serum albumin. Several subgroups were found to be at increased risk of hypoalbuminaemia, however HIV infection was not associated with low serum albumin. This information could prove useful to the treating orthopaedic surgeon, given the proven detrimental effects of hypoalbuminaemia on patients in the perioperative period.

Hypoalbuminaemia has been investigated in certain subgroups of trauma patients. Low serum albumin levels have been shown to be associated with a 2.5-fold increase in surgical site infection in arthroplasty, hip fracture surgery, musculoskeletal tumour, and spinal surgery. (7) Several authors found significantly increased complication rates in the peri-operative period in patients with hypoalbuminaemia in arthroplasty, ankle fracture, proximal humerus and hip fracture surgery. (8,21–24) These complications included but were not limited to myocardial infarction, sepsis, and infection, repeat surgeries within 30 days, increased hospital length-of-stay and higher total healthcare costs.

A study reviewing 54,215 patients undergoing “major, non-cardiac surgery” compared postoperative mortality and morbidity rates, between patients with preoperative albumin levels above 41g/L and those below 21g/L. Hypoalbuminaemia was associated with an exponential increase in mortality rates from under 1% to 29% and in morbidity rates from 10% to 65%. (11) Results are comparable when reviewing research on hypoalbuminaemia in orthopaedic trauma in both young and geriatric cohorts. Hypoalbuminaemia remains a significant predictor of both morbidity and mortality. (10,12)

Two studies reviewed the prevalence of hypoalbuminaemia in patients with hip fractures and found rates of 18% and 46%, respectively. (23,24) In our series 59% of patients

presenting with hip fractures had low serum albumin, imparting a 4.7 times increased risk for hypoalbuminemia. One series found 21% of patients with ankle fractures requiring surgery had hypoalbuminaemia, similar to 28% found in this study. (8)

A literature search revealed little evidence on serum albumin levels in orthopaedic trauma patients in the developing world setting. Most of the existing research has emanated from the developed world and data from Africa remains lacking. Furthermore, there is little data available on the impact of HIV infection on the prevalence of hypoalbuminaemia in LMICs. Only one relevant paper was found with an African setting. This was done in Tanzania and found a 25% prevalence of hypoalbuminaemia in their cohort of femur fractures. (9) Using the same inclusion and exclusion criteria from this research, 46% of femur fracture patients had hypoalbuminaemia in our cohort. Research at a European level one trauma centre found higher hypoalbuminaemia rates than those seen in our cohort (39% vs 29%). They however only looked at patients with diaphyseal femur fractures with the intention to review young patients with high velocity injuries. Their work is consistent with ours with regards to females, the elderly and those with Diabetes Mellitus having increased risk of hypoalbuminaemia. (18)

In this cohort of orthopaedic trauma patients, the mean albumin level was within the normal range. However, certain injury patterns were associated with an increased risk, namely, femoral neck, intertrochanteric femur, and tibial plateau fractures. While open fractures were not associated with hypoalbuminaemia, patients who had sustained polytrauma were. The presence of comorbidities other than HIV was significant in their association with hypoalbuminaemia. These include hypertension, diabetes mellitus, chronic renal failure, and previous pulmonary tuberculosis.

HIV/AIDS is highly prevalent in South Africa (13.1%) and especially in KwaZulu-Natal (27%). (19) In this series HIV infection alone was not associated with hypoalbuminaemia. Our data showed a lower mean albumin value for HIV positive patients (35.7g/L) compared to HIV negative patients (37.5g/L). Hypoalbuminaemia was found in 38% in HIV positive individuals vs. 26% of HIV negative individuals. Although this was not a statistically significant difference ($p = 0.064$) there was a trend for lower albumins in HIV positive patients. Previous research

on albumin levels in asymptomatic HIV positive patients not on ARV therapy found "borderline low" mean albumin levels of 36.1g/L.(25) These results are in contrast to two other studies which showed normal mean albumin levels in asymptomatic HIV infected patients, who were ARV therapy naïve.(26,27) Despite the serum albumin levels being considered normal in both the above mentioned cohorts, it was noted that these levels were significantly lower than both of their HIV uninfected control groups. What all three of the above-mentioned studies have in common is lower serum albumin levels in HIV infected people who are treatment naive. In our study, 92% of patients who were HIV infected were already on ARV therapy. This meant only six patients were HIV infected but not on treatment. Despite the small sample size, the mean albumin for these six patients was 34g/L, in keeping with the studies above.

A long-term study on ischaemic heart disease (mean follow up 25.6 years) recorded serum album levels and risk of fracture (defined as hip, humerus and wrist fractures) and noted that low serum albumin was associated with an increased risk long term fractures in this cohort. (28) This data infers a potential benefit in using albumin as a predictor of long-term fracture risk.

Serum albumin is an inexpensive, readily available blood test which can be used as a prognostic tool to predict the risk of in hospital complications in the orthopaedic trauma patient. It could be used as a screening tool in the high-risk subgroups identified in this series. This insight may allow the treating orthopaedic surgeon an opportunity to better prepare for patients who are hypoalbuminaemic and potentially avoid significant morbidity and mortality.

Limitations to this paper include a relatively small sample size and therefore even smaller numbers when exploring subgroups of patients. All work was based in Northern Kwa-Zulu Natal and this may not be representative of all rural communities in South Africa in terms of patient nutrition, trauma burden and HIV prevalence. There was a lack of standardization in terms of the timing of the serum albumin blood test in relation to their injury and admission. All bloodwork was done on admission; however, in some cases this was several days after the date of injury. Only patients who were admitted for surgery were included

and this may result in a selection bias. However, hypoalbuminaemia is more relevant in this group of patients due to the known increase in peri-operative complications.

Conclusion

Nearly 1/3rd of this cohort of orthopaedics trauma patients from rural South Africa had hypoalbuminaemia at the time of presentation. High risk subgroups include patients with pre-existing comorbidities and increased age, as well as patients presenting with femoral neck, intertrochanteric femur and tibial plateau fractures and patients that sustained polytrauma. While HIV infection alone was not associated with hypoalbuminaemia, patients with other comorbidities may be at increased risk.

Further research on this topic may include a similar analysis of HIV infected patients but with a larger sample size to ascertain if the trend towards a lower serum albumin may become statistically significant.

After the treating orthopaedic surgeon identifies a patient with low serum albumin, future studies could determine what should be done next. Should surgery be delayed while the albumin levels are optimised? Will this delay to theatre have other complications? How quickly can serum albumin levels be raised, and will the increase have meaningful outcomes? Should the treatment plan for patients with hypoalbuminaemia be adjusted i.e., extensive open reconstructive procedures be deferred for more minimally invasive treatment options?

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Haagsma JA, Graetz N, Bolliger I, Naghavi M, Higashi H, Mullany EC, et al. The global burden of injury: Incidence, mortality, disability-adjusted life years and time trends from the global burden of disease study 2013. Inj Prev. 2016;22(1):3–18.

2. Matzopoulos R, Prinsloo M, Pillay-Van Wyk V, Gwebushe N, Mathews S, Martin LJ, et al. Injury-related mortality in South Africa: a retrospective descriptive study of postmortem investigations. Bull World Heal Organ. 2015;93:303–13.

3. Norman R, Matzopoulos R, Groenewald P, Bradshaw D. The high burden of injuries in South Africa. Bull World Health Organ. 2007;85(9):695–702.

4. Gosselin RA, Spiegel DA, Coughlin R, Zirkle LG. Injuries: The neglected burden in developing countries. Bull World Health Organ. 2009;87(4):246.

5. Jain S, Gautam V, Naseem S. Acute-phase proteins: As diagnostic tool [Internet]. Vol. 3, Journal of Pharmacy and Bioallied Sciences. Wolters Kluwer -- Medknow Publications; 2011 [cited 2021 Jan 20]. p. 118–27. Available from: /pmc/articles/PMC3053509/?report=abstract

6. Gounden V, Vashisht R, Jialal I. Hypoalbuminemia [Internet]. StatPearls. StatPearls Publishing; 2020 [cited 2021 Jan 20]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30252336

7. Yuwen P, Chen W, Lv H, Feng C, Li Y, Zhang T, et al. Albumin and surgical site infection risk in orthopaedics: A meta-analysis. BMC Surg [Internet]. 2017;17(1). Available from: http://dx.doi.org/10.1186/s12893-016-0186-6

8. Barber C, Chung A, Jones C, Russell G, Karr S. Effect of Hypoalbuminemia on Perioperative Complications and Hospital Outcomes in Ankle Fracture Fixation. Foot Ankle Orthop. 2017;2(3):2473011417S0000.

9. Masatu DM. Predictive values of serum nutritional indices for early postoperative wound infections in surgically treated closed femoral fractures. SA Orthop J. 2010;9(4):63–7.

10. Garwe T, Albrecht RM, Stoner JA, Mitchell S, Motghare P. Hypoalbuminemia at admission is associated with increased incidence of in-hospital complications in geriatric trauma patients. Am J Surg. 2016;212(1).

11. Gibbs J. Preoperative Serum Albumin Level as a Predictor of Operative Mortality and Morbidity. Arch Surg. 1999;134(1):36.

12. Wilson JM, Lunati MP, Grabel ZJ, Staley CA, Schwartz AM, Schenker ML. Hypoalbuminemia Is an Independent Risk Factor for 30-Day Mortality, Postoperative Complications, Readmission, and Reoperation in the Operative Lower Extremity Orthopaedic Trauma Patient. J Orthop Trauma. 2019;33(6):284–91.

13. Eka A, Chen AF. Patient-related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med. 2015;3(16).
14. Ernst A, Wilson JM, Ahn J, Shapiro M, Schenker ML. Malnutrition and the orthopaedic trauma patient: A systematic review of the literature. J Orthop Trauma. 2018;32(10):491–9.
15. Ellsworth B, Kamath AF. Malnutrition and Total Joint Arthroplasty. J Nat Sci [Internet].2016;2(3):2–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27376151%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4926871
16. Luchetti TJ, Chung A, Olmscheid N, Bohl DD, Hustedt JW. Hypoalbuminemia Is Associated With Increased Postoperative Mortality and Complications in Hand Surgery. Hand. 2020;15(4).
17. Ryan S, Politzer C, Fletcher A, Bolognesi M, Seyler T. Preoperative hypoalbuminemia predicts poor short-term outcomes for hip fracture surgery. Orthopedics. 2018;41(6).
18. Egbert RC, Bouck TT, Gupte NN, Pena MM, Dang KH, Ornell SS, et al. Hypoalbuminemia and obesity in orthopaedic trauma patients: Body Mass Index a Significant Predictor of Surgical Site complications. 2020; Available from: https://doi.org/10.1038/s41598-020-58987-4
19. Mid-year population estimates 2018 StatsSA [Internet]. [cited 2021 Jan 20]. Available from: https://www.statssa.gov.za/publications/P0302/P03022018.pdf
20. Madadeni Provincial Hospital [Internet]. [cited 2021 Jan 20]. Available from: http://www.kznhealth.gov.za/madadenihospital.htm
21. Kishawi D, Schwarzman G, Mejia A, Hussain AK, Gonzalez MH. Low Preoperative Albumin Levels Predict Adverse Outcomes After Total Joint Arthroplasty. J Bone Joint Surg Am. 2020;102(10):889–95.
22. Althoff AD, Ignozzi AJ, Bell JE, Werner BC. Pre-operative Hypoalbuminemia Is Associated with Complications Following Proximal Humerus Fracture Surgery: An Analysis of 919 Patients. HSS J. 2020.
23. Koval KJ, Maurer SG, Su ET, Aharonoff GB, Zuckerman JD. The effects of nutritional status on outcome after hip fracture. J Orthop Trauma. 1999;13(3).
24. Bohl DD, Shen MR, Hannon CP, Fillingham YA, Darrith B, Valle CJD. Serum albumin predicts survival and postoperative course following surgery for geriatric hip fracture. J Bone Jt Surg - Am Vol. 2017;99(24).
25. Biggs C, Spooner E. Obesity and HIV: A compounding problem. South African J Clin Nutr [Internet]. 2018;31(4):78–83. Available from: https://doi.org/10.1080/16070658.2017.1404299
26. Hattingh Z, Walsh C, Veldman FJ, Bester CJ. The metabolic profiles of HIV-infected and non-infected women in Mangaung, South Africa. South African J Clin Nutr. 2009;22(1):23–8. 27.

Oosthuizen W, Van Graan A, Kruger A, Vorster HH. Polyunsaturated fatty acid intake is adversely related to liver function in HIV-infected subjects: The THUSA study. Am J Clin Nutr. 2006;83(5):1193–8.

28. Kunutsor SK, Voutilainen A, Whitehouse MR, Seidu S, Kauhanen J, Blom AW, et al. Serum Albumin and Future Risk of Hip, Humeral, and Wrist Fractures in Caucasian Men: New Findings from a Prospective Cohort Study. Med Princ Pract. 2019;28(5):401–9.

Table 1: Demographic and baseline clinical characteristics of the cohort.

Characteristic	Mean (SD)	n (%)
Age	42.5 ± 1.1	
Male gender		177 (60)
Albumin	37.0 ± 5.6	
Haemoglobin	12.8 ± 0.1	
HIV negative		193 (65)
HIV status unknown		30 (10)
HIV positive patients on ARV		66 (22)
Comorbidities:		
None		150 (51)
HIV positive		72 (24)
Hypertension		40 (14)
Diabetes Mellitus		14 (5)
COPD		3 (1)
Previous TB		15 (5)
Substance abuse		3 (1)
Chronic renal failure		4 (1)
Multiple comorbidities		30 (10)

Table 2: Injury characteristics of the cohort.

Characteristic	n (%)
Injury patterns:	
Polytrauma	42 (14%)
Multiple orthopaedic injuries	25 (8%)
Gunshot wounds	5 (2%)
Open injuries	101 (34%)
Specific injuries:	
Acromion fracture	1 (<1%)
Clavicle fracture	1 (<1%)
Proximal humerus fracture	2 (<1%)
Humerus shaft fracture	6 (2%)
Distal humerus fracture	14 (5%)
Olecranon fracture	5 (2%)
Radius and Ulna shaft fracture	17 (6%)
Distal radius fracture	17 (6%)
Distal ulna fracture	8 (3%)
Carpal fractures of dislocations	1 (<1%)
Hand fracture	27 (9%)
Flexor tendon injuries	10 (3%)
Extensor tendon injuries	9 (3%)
Cervical spine injury	2 (<1%)
Thoracolumbar injuries	3 (1%)
Acetabulum fracture	6 (2%)
Pelvis fracture	6 (2%)
Hip dislocation	4 (1%)
Femur neck fracture	25 (8%)
Intertrochanteric femur fracture	19 (6%)
Femur shaft fracture	23 (8%)
Distal femur fracture	17 (6%)
Patella fracture or tendon injury	7 (2%)
Knee dislocation/ligament injury	4 (1%)
Tibial plateau fracture	15 (5%)
Tibial shaft fracture	26 (9%)
Tibial plafond fracture	11 (4%)
Ankle fracture	32 (11%)
Foot Fractures	6 (2%)
Finger or toe amputations	4 (1%)
Major lacerations or degloving	3 (1%)

Table 3: Comparison of selected risk factors in patients with and without hypoalbuminemia.

Risk factor	Patients with hypoalbuminemia n (%)	Patients without hypoalbuminemia n (%)	p-value
Patient factors			
Age (>65)	27/77 (35%)	23/188 (12%)	**<0.001**
Male	43/86 (50%)	134/209 (64%)	**0.025**
Multiple comorbidities [i]	13/18 (72%)	73/277 (26%)	**<0.001**
Diabetes Mellitus	10/14 (71%)	76/281 (27%)	**<0.001**
Hypertension	17/40 (43%)	69/255 (27%)	0.046
HIV infection	27/72 (38%)	52/193 (27%)	0.095
Nature of trauma			
Open fracture	24/101 (24%)	62/194 (32%)	0.142
Polytrauma	19/42 (45%)	67/253 (26%)	**0.013**
Type of fracture			
Ankle fracture	7/32 (22%)	79/263 (30%)	0.337
Neck of femur fracture	15/25 (60%)	71/270 (26%)	**<0.001**
Peritrochanteric femur fracture	11/19 (58%)	75/276 (27%)	**0.004**
Femur shaft fracture	8/23 (35%)	78/272 (29%)	0.536
Distal humerus fracture	3/14 (21%)	89/281 (30%)	0.515
Tibial plateau fracture	8/15 (53%)	78/280 (28%)	**0.034**
Tibial shaft fracture	6/26 (23%)	80/269 (30%)	0.475

i) Other than HIV infection.

Table 4: Multivariate logistic regression analysis of risk factors associated with hypoalbuminemia.

Risk Factors	Odds Ratio	95% CI	p value
Male sex	0.81	0.42 - 1.55	0.516
Age	**1.02**	**1.00 - 1.04**	**0.022**
Femur neck fractures	2.51	0.90 - 6.98	0.077
Intertrochanteric fractures	2.51	0.82 - 7.74	0.107
Tibial Plateau fractures	**4.14**	**1.22 - 13.97**	**0.022**
Polytrauma	**5.34**	**2.29 - 12.47**	**<0.001**
HIV positive	1.87	0.94 - 3.72	0.073
Presence of comorbidity	**3.48**	**1.61 - 7.51**	**0.001**

Appendices

1. UHERB ethics approval certificate
2. HREC ethics approval certificate
3. DRC approval certificate
4. Accepting journal – comments from the editor
    a. Screen shot
    b. Full text copy and pasted

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Umgungundlovu Health Ethics
Research Board (UHERB)

Reference: UHERB181001
Enquiries: Ms N. Makhathini, 033 395 2102
Date: 13 April 2019

Dear Dr Maimin

RE: APPROVAL OF SUBMITTED STUDY:
Development of Orthopaedic Database at Madadeni Hospital

UHERB has pleasure in informing you that your study has been granted full ethical approval.
In order to proceed with conducting the study, the following is required:

i. Institutional support from the participating study sites
ii. Provincial Health Research and Ethics Committee (PHREC) approval. Application is done online on the National Health Research Database (NHRD) website: www.nhrd.hst.org.za . You will need to register and obtain a username and password before registering your application online. Please go to: "Request use of Provincial facilities".
iii. Upload all the necessary documents.
iv. Submit a report upon completion of the study.

This approval is valid for a period of twelve months only starting from the date the approval is granted. This approval maybe withdrawn at time if a situation arises requiring this.

You are requested to electronically, submit an annual report of your study to this Board.

You are also requested to report to this Board anything that might warrant reconstruction of ethical approval of the protocol including but not limited to:

- Serious or unexpected adverse effects to participants
- Proposed changes to the protocol
- Unforeseen events that might affect continued ethical acceptability of the project

You are requested to inform the Board if the project is terminated or suspended before anticipated date of completion.

We wish you well on your study.

Regards,

Dr Damian Clarke
FCS (SA) MBA, M Med Sci, MBA, M Phil, Phd
Chairperson, UHERB

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 February 2021

HREC REF: 063/2021

Prof M Laubscher
Department of Orthopaedics
H-Floor OMB
Email: maritz.laubscher@uct.ac.za
Student: danemaimin@gmail.com

Dear Prof Laubscher

PROJECT TITLE: HIGH RATES OF UNDIAGNOSED HYPOALBUMINAEMIA IN ORTHOPAEDIC TRAUMA PATIENTS AT A RURAL HOSPITAL-MMED CANDIDATE DR DANE MAIMIN

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 28 February 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Dane Maimin will also be involved in this study.

Please quote the HREC REF 063/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

Department of Surgery
Departmental Research Committee
Dr Timothy Pennel
D24 Office, Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 3430
Email: tim.pennel@uct.ac.za

2 Nov 2020

Dr D Maimin

Department of Surgery
University of Cape Town

Dear Dr Maimin

RE: Project 2020/147

PROJECT TITLE: High Rates Of Undiagnosed Hypoalbuminaemia In Orthopaedic Trauma Patients At A Rural Hospital

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

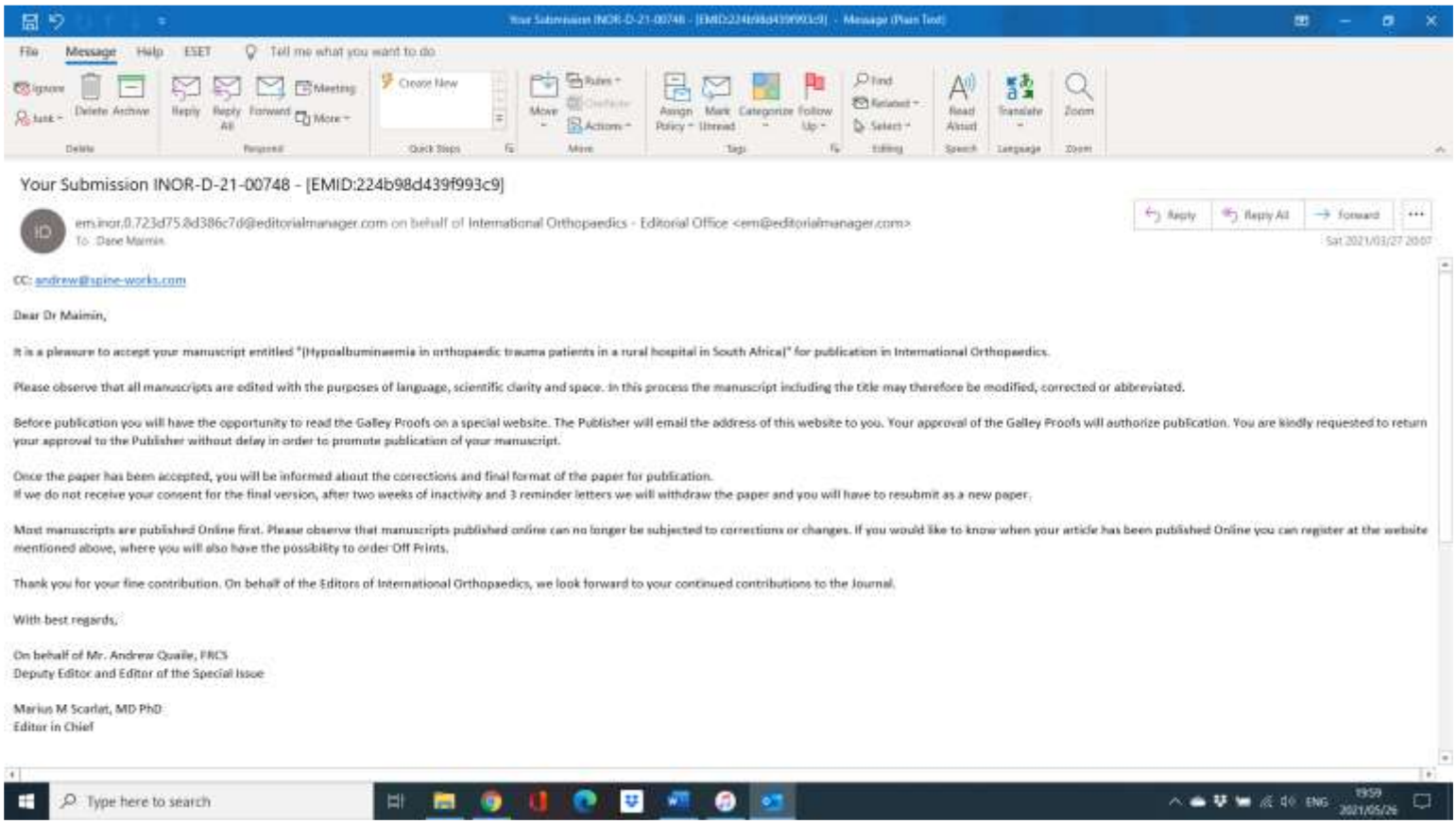
Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

Yours sincerely

DR TIMOTHY PENNEL
CHAIR: SURGICAL DRC

DR MARITZ LAUBSCHER
CHAIR: PROTOCOL REVIEW COMMITTEE



Your Submission INOR-D-21-00748 - [EMID:224b98d439f993c9]

em.inor.0.723d758d386c7d@editorialmanager.com on behalf of International Orthopaedics - Editorial Office <em@editorialmanager.com>
To: Dare Maimin

Reply | Reply All | Forward

Sat 2021/03/27 20:07

CC: andrew@spine-works.com

Dear Dr Maimin,

It is a pleasure to accept your manuscript entitled "(Hypoalbuminaemia in orthopaedic trauma patients in a rural hospital in South Africa)" for publication in International Orthopaedics.

Please observe that all manuscripts are edited with the purposes of language, scientific clarity and space. In this process the manuscript including the title may therefore be modified, corrected or abbreviated.

Before publication you will have the opportunity to read the Galley Proofs on a special website. The Publisher will email the address of this website to you. Your approval of the Galley Proofs will authorize publication. You are kindly requested to return your approval to the Publisher without delay in order to promote publication of your manuscript.

Once the paper has been accepted, you will be informed about the corrections and final format of the paper for publication.
If we do not receive your consent for the final version, after two weeks of inactivity and 3 reminder letters we will withdraw the paper and you will have to resubmit as a new paper.

Most manuscripts are published Online first. Please observe that manuscripts published online can no longer be subjected to corrections or changes. If you would like to know when your article has been published Online you can register at the website mentioned above, where you will also have the possibility to order Off Prints.

Thank you for your fine contribution. On behalf of the Editors of International Orthopaedics, we look forward to your continued contributions to the Journal.

With best regards,

On behalf of Mr. Andrew Quaile, FRCS
Deputy Editor and Editor of the Special Issue

Marius M Scarlat, MD PhD
Editor in Chief

Your Submission INOR-D-21-00748 - [EMID:224b98d439f993c9]

Albumin study

International Orthopaedics - Editorial Office <em@editorialmanager.com> Sat, 27 Mar 2021, 20:07

to me

CC: andrew@spine-works.com

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With best regards,

On behalf of Mr. Andrew Quaile, FRCS
Deputy Editor and Editor of the Special Issue

Marius M Scarlat, MD PhD
Editor in Chief

Dear Author
An interesting paper for our special issue

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Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

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