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Clinical and Experimental Study of Low Molecular Weight Heparin in Patients with Chronic Anemia

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Abstract

Objective: To preliminary study the significance of low molecular weight heparin (LMWH) in the treatment patients of with anemia of chronic diseases (ACD), and the changes in the serum levels of BMP6, hepcidin and IL-6. To preliminary study the significance of low molecular weight heparin (LMWH) in the treatment the patients with anemia of chronic diseases (ACD), and the changes in the serum levels of BMP6, hepcidin and IL-6. **Methods:** Used LMWH (4000 u/day, 7 - 15 days) to therapy 61 patients with ACD, and ELISA method was used to determine Hepcidin and BMP6 before and after treatment, and the determination of IL-6 by Electro-chemi-luminescence, and to analyze its clinical significance. **Results:** 1) In all 61 cases, the levels of Hepcidin in post-therapy were 0.82 ± 0.24 mg/L, which were lower than 1.05 ± 3.83 mg/L in pre-therapy (t = 2.5726, $P < 0.05$). The levels of IL-6 in post-therapy were 24.88 ± 12.58 mg/L, which were lower than 38.22 ± 31.23 mg/L in pre-therapy (t = 2.9650, $P < 0.05$), but there were no statistically significant both Hb and BMP6 between in pre-therapy and post-therapy (all $P > 0.05$). However, The levels of Hb in post-therapy were higher than in pre-therapy (t = 1.9832, $P < 0.05$). 2) The Hb level in the tumor anemia group after treatment was 91.18 ± 15.91 g/L, which was higher than that before treatment (85.45 ± 18.33 g/L), the difference was statistically significant (t = 1.9711, $P < 0.05$). 3) The levels of hepcidin and IL-6 in the tumor anemia group after treatment were 0.73 ± 0.45 mg/L and 30.33 ± 28.39 mg/ml, which were lower than those before treatment (1.09 ± 0.41 mg/L and 50.76 ± 42.10 mg/ml), respectively, the difference was statistically significant (t = 3.3941, $P < 0.01$ and t = 2.3597, $P < 0.05$). 4) There was no significant difference in all indexes in tumor anemia free group (all $P > 0.05$). 5) Although Hb level increased

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slightly in the non-tumor anemia group, there was no statistical significance ($P > 0.05$), and there was no statistical difference in other indexes (all $P > 0.05$). 6) After treatment, the level of Hb was negatively correlated with Hepcidin and IL-6 (respectively r = −0.2809, t = 2.2490, $P < 0.05$ and r = −0.2781, t = 2.2266, $P < 0.05$). Hepcidin was positively related to IL-6 (r = −0.2941, t = 2.3622, $P < 0.05$). There was no correlation between BMP6 and Hb, Hepcidin and IL-6 levels. **Conclusion:** LMWH could up-regulate the levels of Hb, and better for the degree of anemia in patients with ACD. The possible mechanism is to reduce the level of Hepcidin and IL-6.

Keywords

Anemia of Chronic Disease, BMP6, Hepcidin, IL-6, Hemoglobin, Low Molecular Weight Heparin, Therapy

1. Introduction

At present, it has been confirmed that the inflammatory response of patients with chronic anemia (anemia of chronic disease, ACD) leads to the high expression of interleukin-6 (interleukin-6, IL-6) and the high expression of ferritin (also known as a liver antimicrobial polypeptide, Hepcidin, referred to as Hep), and finally leads to anemia. However, the treatment of ACD is very difficult. Recently, it has been reported that heparin can improve anemia in ACD. The mechanism may be that heparin down-regulates the expression of Hep through the bone morphogenic protein 6 (bone morphogenetic protein 6, BMP6) pathway. The observation that BMPs are heparin-binding molecules and that heparin modifies the osteogenic activity of BMP2/4 stimulated (Poli *et al.*, 2011) to verify the effect of heparin on hepcidin expression. It was shown that commercial heparins are potent hepcidin inhibitors *in vitro* in HepG2 cells and *in vivo* in healthy mice and that act by inhibiting the BMP6/SMAD signaling. Heparins are well-characterized molecules with some 70 years of clinical experience, and appealing drugs for the treatment of anemia. However, there are few studies on this aspect in our country. Based on early clinical observation of low molecular weight heparin (low molecular weight Heparin, LMWH) in the treatment of tumor-associated anemia, we further observed the changes of hemoglobin (Hb) level, BMP6, IL-6, and Hepcidin in patients with ACD after LMWH treatment. To analyze the clinical significance and possible mechanism of LMWH in the treatment of ACD.

2. Materials and Methods

2.1. Research Object

There were 61 inpatients in our hospital from January 2016 to June 2018, including 32 males and 29 females, aged 33 - 90 years, with an average age of 61.7 years. All patients were treated with LMWH because of thrombosis or high

plasma D-dimer with thrombotic tendency. The types of diseases were as follows: 1) 43 cases of malignant tumors (including 11 cases of lung cancer, 8 cases of gastric cancer, 5 cases of colorectal cancer, 5 cases of ovarian cancer, 3 cases of lymphoma, 3 cases of prostate cancer, 2 cases of breast cancer, 2 cases of liver cancer, 2 cases of pancreatic cancer and 2 cases of cervical cancer). 2) there were 18 cases of non-tumor diseases (including 10 cases of acute myocardial infarction and acute coronary syndrome, 6 cases of varicose veins with thrombosis of lower extremities, 1 case of severe pneumonia, and 1 case of pulmonary embolism). 3) the cases of malnutrition and chronic hepatorenal diseases with obvious influence on iron metabolism have been excluded, and the cases of less than 7 days of heparin treatment have also been removed.

2.2. Reagents and Instruments

1) Reagents are purchased from DiaSys Diagnostic System Gmb, including human hepc ELISA Kit (96T) and Elecsys and codebase analyzers (IL-6. 100T) and Human Bone Morphogenetic Protein 6ELISA kit (96T), etc. 2) The detection instrument used is the enzyme labeling instrument of American BioTex Company, the electro-chemi-luminescence instrument of ELx800; Roche Company, and the model COBAS601.

2.3. Research Methods

1) Grouping method: the patients were divided into tumor group and non-tumor group, and each group was divided into anemia group and non-anemic group according to the level of Hb. There were 43 cases in the tumor group, including 33 cases of anemia and 10 cases of no anemia, 18 cases of the non-tumor group, 9 cases of anemia, and 9 cases of non-anemia. The diagnostic criteria of anemia were Hb < 120.0 g/L in males and <110.0 g/L in females. 2) low molecular weight heparin therapy: farming (Pfizer) or enoxaparin (Hangzhou Jiuyuan Gene Biology Co., Ltd.) were used for 4000 u/days, subcutaneously injected for 7 - 15 days for at least 7 days. Blood samples were taken to detect Hb on the day before treatment and the day after treatment. 3) Test method: the blood samples of fasting patients were taken in the early morning and stored in different test tubes, stored in a refrigerator at −80˚C, and monitored centrally at the same time. Hepcidin and BMP6 were detected by the ELISA method and IL-6, Hb was detected by the electro-chemi-luminescence method.

2.4. Statistical Analysis

SPSS19.0 software package was used for statistical analysis. T-test and correlation analysis were used respectively. *P*-value < 0.05 was considered to be statistically significant.

3. Results

The results of Hb level and various detection indexes of all 61 patients before

and after LMWH treatment are shown in Table 1. Hb and BMP6, Hepcidin, and IL-6 were measured before and after LMWH treatment. The level of Hepcidin, IL-6 after treatment was lower than that before treatment, and the difference was statistically significant ($P < 0.05$), but there was no significant difference between Hb and BMP6 ($P > 0.05$).

The level of Hb and the detection results of various indexes in tumor and non-tumor patients before and after LMWH treatment are shown in Table 2. Considering the difference between the nature of the tumor and non-tumor disease, the two were compared and analyzed respectively. The Hb level in the tumor anemia group after treatment was 91.18 ± 15.91 g/L, which was higher than that before treatment (85.45 ± 18.33 g/L), the difference was statistically significant (t = 1.9711, $P < 0.05$). The levels of hepcidin and IL-6 in the tumor anemia group after treatment were 0.73 ± 0.45 mg/L and 30.33 ± 28.39 mg/ml, which were lower than those before treatment (1.09 ± 0.41 mg/L and 50.76 ± 42.10 mg/ml), respectively, the difference was statistically significant (t = 3.3941, $P < 0.01$ and t = 2.3597, $P < 0.05$). There was no significant difference in all indexes in the tumor anemia-free group (all $P > 0.05$). Although the Hb level increased slightly in the non-tumor anemia group, there was no statistical significance ($P > 0.05$), and there was no statistical difference in other indexes (all $P > 0.05$).

The correlation analysis is shown in Table 3. The correlation between Hb level and BMP6, IL-6, and Hepcidin in 61 patients after treatment was analyzed. The results showed that 1) there was a negative correlation between Hb level and IL-6 and Hepcidin, but no correlation with BMP6. 2) IL-6 was positively correlated with Hepcidin, but not with BMP6.

Table 1. Determination results of various indexes in all 61 patients before and after treatment ($\bar{\chi} \pm S$).

Item	Subgroup	n	Before treatment	After treatment	t	*P*
Hb (g/L)		61	96.62 ± 25.24	98.67 ± 21.59	0.8482	>0.05
	anemia	42	84.57 ± 27.13	89.74 ± 25.26	1.9832	<0.05
	Non-anaemia	19	123.26 ± 31.12	118.37 ± 21.19	1.5866	>0.05
BMP6 (mg/ml)		61	162.49 ± 86.35	158.61 ± 81.01	0.3424	>0.05
	anemia	42	173.70 ± 82.33	168.66 ± 83.08	0.9647	>0.05
	Non-anaemia	19	137.72 ± 66.23	136.39 ± 71.25	0.0158	>0.05
Hepcidin (mg/L)		61	1.02 ± 3.83	0.82 ± 0.24	2.5726	<0.05
	anemia	42	1.05 ± 3.96	0.74 ± 0.19	2.9865	<0.01
	Non-anaemia	19	0.94 ± 3.22	0.96 ± 0.31	0.3514	>0.05
IL-6 (mg/ml)		61	38.22 ± 31.23	24.88 ± 12.58	2.9650	<0.01
	anemia	42	43.96 ± 33.42	26.60 ± 23.36	2.6715	<0.01
	Non-anaemia	19	33.42 ± 23.17	17.88 ± 13.18	3.1688	<0.01

Table 2. Results of determination of various indexes in tumor and non-tumor patients before and after treatment.

Item	Tumor group (n = 43)						Non-tumor group (n = 18)					
	Anemia group (n = 33)			Non-anemia group (n = 10)			Anemia group (n = 9)			Non-anemia group (n = 9)		
	Before treatment	After treatment	t	Before treatment	After treatment	t	Before treatment	After treatment	t	Before treatment	After treatment	t
Hb (g/L)	85.45 ± 18.33	91.18 ± 15.91	1.9711*	122.80 ± 7.08	118.40 ± 11.47	1.0320	81.33 ± 39.04	84.44 ± 37.27	0.1729	123.78 ± 47.34	118.33 ± 47.17	0.2446
BMP6 (mg/ml)	172.60 ± 99.80	167.76 ± 94.00	0.1838	155.74 ± 47.10	151.42 ± 37.48	0.2270	177.74 ± 77.69	171.96 ± 88.19	0.1312	117.69 ± 59.17	119.69 ± 59.17	0.0480
Hepcidin (mg/L)	1.09 ± 0.41	0.73 ± 0.45	3.3941#	1.07 ± 0.32	1.07 ± 0.33	0.0010	0.89 ± 0.52	0.80 ± 0.51	0.3721	79 ± 0.41	0.84 ± 0.48	0.2240
IL-6 (mg/ml)	50.76 ± 42.10	30.33 ± 28.39	2.3597*	37.57 ± 45.37	25.29 ± 18.92	1.4334	19.01 ± 15.72	19.72 ± 812.4	0.0809	14.41 ± 12.60	39.64 ± 7.45	1.6015

Note: *$P < 0.05$, #$P < 0.01$, others are $P > 0.05$.

Table 3. Correlation analysis results.

Comparison group	r	*P*	Comparison group	r	*P*
Hb/BMP6	−0.0026	>0.05	Hepcidin/IL-6	0.2941*	<0.05
Hb/Hepcidin	−0.2809*	<0.05	Hepcidin/BMP6	0.0447	>0.05
Hb/IL-6	−0.2781*	<0.05	IL-6/BMP6	0.0770	>0.05

Note: *$P < 0.05$, others are $P > 0.05$.

4. Discussion

Existing studies have shown that malignant tumor is a chronic inflammatory disease, and tumor-associated anemia is a kind of ACD. The high expression of IL-6 and Hepcidin in serum of these patients is the main cause of anemia [1] [2] [3] [4]. However, most of the tumor patients with anemia are actually in the advanced stage and lack effective treatment. Therefore, it is difficult to control the inflammatory state of ACD by treating the primary disease of a tumor. Therefore, the application of anti-IL-6 or anti-Hep in the treatment of ACD is a subject worthy of further study, and it is likely to be the hope for the treatment of tumor ACD [5] [6] [7]. Recently, some foreign scholars (MUARA *et al.*) have observed the changes of Hb in the process of using heparin in some patients with pneumonia and heart disease and then found that it is related to the changes of Hepcidin level and Hb level [8].

This study showed that the level of Hb in the tumor anemia group after treatment was 91.18 ± 15.91 g/L, which was higher than that before treatment (85.45 ± 18.83 g/L) (t = 1.971, $P < 0.05$). At the same time, the levels of IL-6 and Hepcidin were significantly lower than those before treatment, and the difference was statistically significant (t = 2.3597, $P < 0.05$ and t = 3.3941, $P < 0.01$). This is consistent with the results of our recently reported study [9]. Further research and analysis showed that the levels of IL-6 and Hepcidin were negatively correlated with Hb levels, while the levels of IL-6 and Hepcidin were positively

correlated. This result is consistent with our previous research results; it is also consistent with the results of MAURA *et al.*, and MAURA *et al.* found that Hepcidin decreased significantly in all subjects after the administration of heparin (but they did not detect IL-6), indicating that heparin can increase the level of Hb in tumor patients and improve the state of anemia.

At the same time, this study also observed the changes of various indexes in 18 non-tumor patients after using LMWH, but except for the slight increase of Hb level in the anemia group, the differences of all other indexes were not statistically significant, which was different from the results of MUARA *et al.* The reason for the analysis may be related to different types of diseases, including 3 cases of pneumonia, 1 case of chronic heart failure and 1 case of chronic heart failure complicated with pneumonia, while we are mainly acute diseases of acute myocardial infarction, acute coronary syndrome and vascular diseases of lower extremities. At the same time, the further study found that the serum IL-6 level of the 18 non-tumor patients was generally lower than that of tumor ACD patients, suggesting that the inflammatory state of the body is not serious.

Foreign studies have shown that heparin can improve anemia mainly through BMP6 down-regulating the level of Hepcidin [10] [11]. The mechanism may be related to the inhibition of BMP6-mediated Hepcidin expression and the inhibition of the IL-6 pathway to down-regulate the level of Hepcidin. However, we found that although the BMP6 level of tumor ACD patients seemed to be higher than that of non-tumor patients, there was no significant difference in BMP6 levels between anemic and non-anemic patients before and after treatment (all $P > 0.05$). There was no correlation between BMP6 and the levels of Hepcidin and Hb (all $P > 0.05$), suggesting that the mechanism of anemia may not be the same as that of other ACD in patients with tumor ACD and patients with acute cardiovascular disease without chronic inflammation. We will further study the exact significance of the different expressions of BMP6 in tumor ACD patients and non-tumor patients.

In addition, this study found that the improvement of the Hb level of patients by LMWH was not as obvious as that reported in the literature. The possible reasons were related to different heparin preparations. LMWH was used in this study. It is reported that unfractionated heparin is used in literature. This study shows that unfractionated heparin has a strong dose-dependent effect. Unfractionated heparin is about 10 times more potent than LM-WH, that is, the ability to increase the level of Hb is in the following order: unfractionated heparin (molecular weight 12 - 15 kDa) > enoxaparin (4.5 kDa) > pentasaccharide sulfa heparin (1.7 kDa). We also need to focus on adverse reactions, because our patient may still have had an underlying coagulopathy. For example, unfractionated heparin may have placed the patient at an increased risk for an epidural hematoma. This is especially prudent in the setting of TID-dosed subcutaneous heparin [12].

In a word, LMWH can improve the anemia of tumor ACD patients to some extent by down-regulating the levels of IL-6 and Hepcidin, which is worthy of

further study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Pan, X.T., Lu, Y., Cheng, X., *et al.* (2016) Hepcidin and Ferroportin Expression in Breast Cancer Tissue and Serum and Their Relationship with Anemia. *Current Oncology*, **23**, 24-26. https://doi.org/10.3747/co.23.2840

[2] Zhang, A.S., Yang, F., Wang, J.M., *et al.* (2009) Hemojuvelin-Neogenin Interaction Is Required for Bone Morphogenic Protein-4-Induced Hepcidin Expression. *Journal of Biological Chemistry*, **284**, 22580-22589. https://doi.org/10.1074/jbc.M109.027318

[3] Nemeth, E. (2010) Targeting the Hepcidin-Ferroportin Axis in the Diagnosis and Treatment of Anemia. *Advances in Hematology*, **2010**, Article ID: 750643. https://doi.org/10.1155/2010/750643

[4] Yan, M., Cheng, X., Lu, Y., *et al.* (2018) The Relationship of Expression Levels of C-Reactive Protein with Serum IL-6 and Anemia in Tumor Patients. *China Continuing Medical Education*, **10**, 76-78.

[5] Akchurin, O., Sureshbabu, A., Doty, S.B., *et al.* (2016) Lack of Hepcidin Ameliorates Anemia and Improves Growth in an Adenine-Induced Mouse Model of Chronic Kidney Disease. *American Journal of Physiology-Renal Physiology*, **311**, F877-F889. https://doi.org/10.1152/ajprenal.00089.2016

[6] Nairz, M., Theurl, I., Wolf, D., *et al.* (2016) Iron Deficiency or Anemia of Inflammation?: Differential Diagnosis and Mechanisms of Anemia of Inflammation. *Wiener Medizinische Wochenschrift*, **166**, 411-423. https://doi.org/10.1007/s10354-016-0505-7

[7] Poli, M., Asperti, M., Ruzzenti, P., *et al.* (2014) Hepcidin Antagonists for Potential Treatments of Disorders with Hepcidin Excess. *Frontiers in Pharmacology*, **5**, 86. https://doi.org/10.3389/fphar.2014.00086

[8] Poli, M., Girelli, D., Campostrini, N., *et al.* (2016) Heparin: A Potent Inhibitor of Hepcidin Expression *in Vitro* and *in Vivo*. *Blood*, **117**, 997-1004. https://doi.org/10.1182/blood-2010-06-289082

[9] Lu, Y., Shao, H., Cheng, X., *et al.* (2019) Preliminary Study on the Effects of Low Molecular Weight Heparin on Hb and C Reactive Protein Levels in Patients with Chronic Anemia. *The Modern Journal of Laboratory Medicine*, **34**, 130-132.

[10] Li, L., Wang, X., Zhang, H., *et al.* (2021) Low Anticoagulant Heparin-Iron Complex Targeting Inhibition of Hepcidin Ameliorates Anemia of Chronic Disease in Rodents. *European Journal of Pharmacology*, **897**, Article ID: 173958. https://doi.org/10.1016/j.ejphar.2021.173958

[11] Maura, P., Michela, A., Paola, R., *et al.* (2017) Non-Anticoagulant Heparins Are Hepcidin Antagonists for the Treatment of Anemia. *Molecules*, **22**, 598. https://doi.org/10.3390/molecules22040598

[12] Abdelfattah, B.A., Buck, T. and Byram, S. (2014) Epidural Hematoma after the Use of Subcutaneous Unfractionated Heparin and History of Epidural Tumor. *Open Journal of Anesthesiology*, **4**, 163-166. https://doi.org/10.4236/ojanes.2014.47023

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Prevalence and Factors Associated with Mortality among Chest Injury Patients Admitted at Muhimbili National Hospital in Dar es Salaam, Tanzania

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Abstract

Introduction: Accidents represent a significant proportional of non-communicable disease in the current century, and chest injury is common. However, management and outcome of these injuries is poor in low resource setting like Tanzania. The aim of this study was to determine the prevalence and factors associated with mortality among chest injury patients at a tertiary level health facility in Tanzania. **Method:** A prospective Cross-Sectional study of chest injuries among trauma patients attended at Muhimbili National Hospital between September 2019 and February 2020. **Results:** A total of 282 trauma patients were seen, out of which 51/282 (18.1%) sustained chest injury. Road Traffic Crashes were the leading cause of chest injury 41/51 (80.4%). Majority 17/51 (33.3%) presented with lung contusion, followed by pneumohemothorax and rib fractures each 8/51 (15.7%). Most of the patients 27/51 (52.9%) were managed by tube thoracostomy and 42.1% conservatively. Mortality was 11/51 (21.6%). Independent factors associated with mortality were: Associated injuries (Odds Ratio (OR) 0.07, 95% CI 0.01 - 1.16, p = 0.02), Multimodal analgesia (Odds Ratio (OR) 0.22, 95% CI 0.05 - 0.98, p = 0.05), more than 24 hours to treatment (Odds Ratio (OR) 5.53, 95% CI 1.25 - 24.3, p = 0.02), Bilateral chest involvement (Odds Ratio (OR) 4.61, 95% CI 1.12 - 18.7, p = 0.02), and Invasive ventilation (Odds Ratio (OR) 31.5, 95% CI 4.47 - 53.8, p = 0.00). **Conclusion:** Chest injuries prevail significantly among trauma patients in Tanzania, mostly due to road traffic crashes. Injury preventive measures especially for road traffic crashes need to be reinforced, and establishment of chest injury management protocol in Tanzania.

Keywords

Chest Injury, Road Traffic Crashes, Tanzania

1. Introduction

Trauma continues to be associated with high morbidity and mortality both in developed and developing countries [1]. Chest Injuries account for 10% of Global trauma admission and 25% of trauma related deaths [2] [3]. Studies have revealed the prevalence of chest injury to be varying from different parts of the world, being high in low- and middle-income countries and low in developed countries [4], this is mostly due to variations in preventive measures of trauma. The estimated mortality due to chest injuries in Tanzania is 40% [5], and continues to be the commonest cause of surgical admissions with significantly high morbidity and mortality [6].

Causes and pattern of chest injuries vary in different parts of the world due to socio-economic status variations, the commonest cause being road traffic crashes [7] [8], majorities of victims being in the active age group sustaining blunt chest injury. Like other developing nations in the world, Tanzania has a significantly high rate of traffic related deaths and disabilities. A hospital-based injury surveillance [9] revealed traffic crashes to be the leading cause of injuries accounting for 47.5% of all injuries seen and 60.5% of injuries mortality. Chest injury is second only to head injury as a major cause of morbidity and mortality in Tanzania emergency rooms, and this can be explained by the lack of organized pre-hospital care, severity of injuries and late management of patients [10].

Management option depends on type of chest injury and clinical presentation of the patients. Patients with pneumothorax, haemothorax or both would improve on tube thoracostomy. Other patients would require mechanical ventilation, appropriate analgesics management, supportive therapy and critical care observation [11] [12]. It is therefore necessary for accurate, early identification and aggressive management of chest injuries, along with prompt treatment of associated injuries for optimal patient outcome. This study was therefore conducted to help us understand the magnitude and management of chest injury patients at a tertiary level health facility in Tanzania. The result of this study will help in establishing prevention strategies as well as management protocol to better assess, treat and monitor chest injury patients with a view of improving patient outcomes.

2. Methodology

Study setting: data were collected from Muhimbili National Hospital emergency medicine department. It is the main government tertiary hospital of Tanzania, located along Dar es Salaam region in Tanzania and has the capacity 1500 beds. It is a referral centre for all other hospitals in Dar es Salaam (over 5 million

inhabitants) and Tanzania at large, and is also a teaching hospital for Muhimbili University of Health and Allied Sciences.

Study design: A prospective Cross-Sectional study was conducted.

Study population: the study population comprised of chest injury patients attended at Muhimbili National Hospital emergency department between September 2019 and February 2020.

Data collection and management: a structured questionnaire designed by principal investigators was used to collect information from the study participants in a face-to-face interview, and from medical records. Questions were drawn from previously conducted studies and a pilot study was conducted to ensure validity and reliability of the data collection tool. A questionnaire had 18 items including: socio-demographic characteristics, mode of injury, type of injury, severity of injury, treatment pattern and patient's outcome (**Appendix**). Data were double-entered into Excel (MicrosoftÂ® Excel, Seattle Washington), Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp. IBM SPSS Statistics for Windows [Internet]. Armonk, NY: IBM Corp; 2017).

Statistical analysis: all variables were categorized and described using frequency distribution. Chi-square test was used for bivariate analysis and those variables with observed frequency less than five Fisher's exact test was applied. A variable with ($p \leq 0.05$) with mortality was considered to be statistically significant. Variables that demonstrated significant bivariate association with mortality were entered into the multivariate logistic regression modal to assess independent effects. Parameter of measurement to assess association was odds ratio.

Ethical consideration: ethical approval for the study was obtained from the Muhimbili University of Health and Allied Sciences Research Ethics Committee. An informed written consent was sought from patients or relatives.

3. Results

A total of 282 trauma patients were seen between September 2019 and February 2020. Chest injuries accounted for 51/282 (18.1%) of patients, majority (72.5%) belonged to the productive age group (20 to 39 years), and 74.5% were males, with a male to female ratio of 3:1 (**Table 1**).

3.1. Mechanism of Injury

Road traffic crashes (80.4%) were responsible for the majority of Chest injuries, Assault (15.7%) and fall from height (3.9%).

3.2. Type of Chest Injuries

Blunt trauma accounted for 88.2% of the chest injuries, 11.8% were penetrating injuries. Lung contusion was the commonest (33.3%) followed by, Pneumohemothorax and Rib fractures each (15.7%). Pneumothorax was present in 11.7% of the patients whereas haemothorax was present in 7.8% of the cases.

Two patients (3.9%) had an injury to the heart and 3.9% had a Flail chest (Table 2). Majority of patients (52.9%) had tube thoracostomy done, and 42.1% managed conservatively.

Table 1. Social demographic characteristics.

Sex	Frequency (n)	Percentage (%)
Male	38	74.5
Female	13	25.5
Total	51	100
Marital status		
Single	27	52.9
Married	21	41.2
Others	3	5.9
Total	51	100
Education		
Primary school	15	29.4
Secondary school	18	35.3
High level	13	25.5
No formal education	5	9.8
Total	51	100
Age (Years)		
1 to 19	2	3.9
20 to 39	37	72.5
40 to 59	11	21.6
60 and above	1	2
Total	51	100

Table 2. Type of chest injury.

Chest injury type	Frequency (percentage)
Pneumothorax	6 (11.7)
Hemothorax	4 (7.8)
Pneumohemothorax	8 (15.7)
Rib fracture	8 (15.7)
Lung contusion	17 (33.3)
Clavicle fracture	4 (7.8)
Cardiac injury	2 (3.9)
Flail chest	2 (3.9)

3.3. Factors Associated with Mortality

Of the 51 patients seen 78.4% survived, and 21.6% died. The following factors were significantly associated with mortality after bivariate analysis: Associated injuries accounted for 63.6% of mortality (p-value 0.014), serious and critical injured patients each accounted for 36.4% of mortality (p-value 0.009), using a single type of analgesia accounted for 72.7% of mortality (p-value 0.038), receiving medical attention 24 hours after injury contributed 72.7% of mortality (p-value 0.016). Bilateral chest involvement contributed 63.6% of mortality (p-value 0.026) and invasively ventilated patients 81.8% of mortality (p-value 0.00) (Table 3).

Table 3. Factors associated with mortality.

Factor	Death N (%)	No death N (%)	P-value	Multivariate OR (95% CI)	P-value
Age (Years)					
1 - 19	1 (50)	1 (50)			
20 - 39	7 (18.9)	30 (81.1)	0.66		
40 - 59	3 (27.3)	8 (72.7)			
60 and above	0 (0.0)	1 (100)			
Sex					
Male	9 (23.7)	29 (76.3)	0.76		
Female	2 (15.4)	11 (84.6)			
Associated injuries					
Present	7 (15.91)	37 (84.09)	0.014^{++}	1	
Not present	4 (57.14)	3 (32.86)		0.07 (0.01 - 1.16)	0.024^{++}
AIS range					
Moderate	1 (14.29)	6 (85.71)		1	
Serious	4 (13.33)	26 (86.67)	0.009^{++}	0.92 (0.08 - 9.8)	0.09
Severe	2 (22.22)	7 (77.78)		1.71 (1.22 - 23.9)	0.68
Critical	4 (80.00)	1 (20.00)		24 (1.14 - 50.5)	0.04^{++}
Pain management					
Single analgesia	8 (34.78)	15 (65.22)	0.038^{++}	1	
More than 1 analgesia	3 (10.71)	25 (89.29)		0.22 (0.05 - 0.98)	0.05^{++}
Time to treatment (hours)					
Less than 24	3 (10.00)	27 (90.00)	0.016^{++}	1	
24 and above	8 (38.89)	13 (61.90)		5.53 (1.25 - 24.3)	0.00^{++}
Chest involvement					
Unilateral	4 (12.12)	29 (87.88)	0.026^{++}	1	
Bilateral	7 (38.89)	11 (61.11)		4.61 (1.12 - 18.7)	0.02^{++}
Assisted ventilation					
Non invasive	2 (5.12)	37 (94.9)	0.00^{++}	1	
Invasive	9 (75)	3 (25)		31.5 (4.47 - 53.8)	0.00^{++}

AIS = abbreviated injury severity score; $^{++}$P-value ≤ 0.05.

The following factors remained statistically significant after multivariate logistic regression analysis: Associated injuries, critical injury, analgesia mode, time to treatment, bilateral chest involvement and invasive ventilation. Those with no associated injuries were 93% less likely to die than those who had associated injuries. Critical injured patients were 24 times more likely to die than moderately injured patients. Presenting to hospital more than 24 hours post-injury were 5.5 times more likely to die compared to those who presented to hospital within 24 hours post-injury. Those with bilateral chest involvement were 4.6 times more likely to die than those who had unilateral chest involvement. The risk of death was 31.5 times greater in those who needed invasive ventilation than non-invasive ventilation, and it was 78% less in those who had more than one analgesia than those managed by a single analgesia (**Table 3**).

4. Discussion

This study aimed at finding the prevalence of chest injuries among trauma patients and the predictors of mortality. The prevalence of chest injuries in this study was 18.1%, similar to what has been reported in other sub-Saharan African countries [11] [12]. This study also revealed majority of injured patients to be males in productive age group, with a male to female ratio of 3:1 similar to other studies in Africa and elsewhere [13] [14]. Male predominance is attributed to their active involvement in the risky daily activities for living, including speeding motorcycles, vehicles, violence and falls. Majority of injured victims in this study were in economically active group (20 - 39 years), this has a direct impact economically on individuals, families, communities and the country at large hence the need for health education aimed at reducing the incidence and severity of trauma targeting this group of people.

Road traffic crashes (80.4%) were responsible for the majority of Chest injuries in this study. Other studies conducted in Tanzania [6] [9] [10] have revealed similar results. Road Traffic Crashes especially motorcycles continue to be a leading cause of trauma and admission of most hospitals in Tanzania, hence a call for road traffic crash prevention measures. World Health Organization notes the escalating road traffic crashes in developing countries, some of the major reasons for this trend are: increasing motorization, poor road infrastructure, not complying to traffic laws and driving or riding under the influence of recreational substances [15] [16].

Majority in this study were blunt injury (88.2%), this is higher than 55.7% reported by Mwesigwa *et al.* in Mbarara, Uganda [17], and is in contrast to two other studies done by Ali, Gali [18] and Maxwell [19], which revealed penetrating injuries to be 61.5% and 77% respectively. Lung contusion (33.3%) was the leading clinical type of chest injury seen in this study; other studies however have reported rib fractures to be the commonest type of chest injury [17] [20] [21]. Otieno *et al.* reported hemopneumothorax to be the commonest injury sustained in the Kenyan rural population [22].

Two patients (3.9%) had Cardiac Injury in this study, similar to what was reported by Masaga *et al.* [20], in which they reported few patients with life threatening conditions such as oesophageal perforation, cardiac injury and diaphragmatic rupture. Majority of victims sustaining these types of severe injuries die at the site of accidents and hence don't make it to hospitals.

Majorities 58.8% of injury victims were attended in within 24 hours from injury in this study, and were more likely to survive than those who received medical attention more than 24 hours from injury. Delay in receiving medical attention minimises the chance of survival for the injured patients, especially severely injured patients. This calls for proper pre-hospital emergency care system and ambulance services in developing countries like Tanzania if severely injured patients are to survive.

Most of the patients (52.9%) in this study, required a chest tube thoracostomy and others (42.1%) were managed conservatively by (observation, analgesia and antibiotics and chest physiotherapy), similar to what has been reported in other studies done elsewhere [6] [23]. It is also reported in studies done in developed countries that observation, chest tube placement, adequate volume replacement, occasional respiratory support and serial chest X-rays are the only treatment required in 80% - 85% of the patients [24] [25].

In this study, 23 (45%) patients were given one type of pain medication and 28 (55%) were given more than one type of pain medication. Pain management option significantly influenced survival, those who received more than 1 type of pain medication were more likely to survive as compared to those who received a single type of pain medication. Results similar to Annalise *et al.* in her review on treatment of chest trauma and their impact [26], in which it was revealed that using more than one option of pain medication improved the outcome of thoracic injury patients. Other studies have demonstrated a big role of regional anaesthesia with intercostal blockade, thoracic epidurals and paravertebral blockades in significant reduction of pain in chest injury patients [6] [27]. The main options in our setting were systemic medication (Opioids, NSAIDS and paracetamol), which have been reported in literatures to be insufficient for optimal pain control [28]. Optimal pain control in chest injury patients prevents splinting of the diaphragm and atelectasis.

In this study, 12 (23.5%) patients needed invasive ventilation and were 31.5 times more likely to die than non-invasive ventilated patients. Patients with blunt or penetrating chest trauma may require mechanical ventilation. Lung protective ventilation strategies have to be applied otherwise it is associated with attributable mortality if it is set incorrectly [29], hence a need for mechanical ventilation modes training for personnel's working in our emergency rooms and intensive care units.

The mortality rate in this study was 21.6% which is almost similar to what was reported by Massaga *et al.* 24.2% [20], but higher compared to what was reported in other studies done elsewhere [6] [17]. Statistically significant predictors of mortality in this study included associated injuries, analgesia mode, time

to treatment, critical injury, bilateral chest involvement and invasive ventilation, results almost similar to what have been reported in other studies done elsewhere [6] [17] [20]. There is therefore a need for management improvement strategies targeting these predictors of mortality in order to improve outcome of chest injury patients in Tanzania, including establishing trauma care system in the country.

In considering the findings of this study it is important to bear in mind the following limitations: firstly, this was a single centre study with small number of patients, and the time frame of the study was short, hence it may not reflect what is happening in other centres. Secondly, data collectors not collecting all data and so some are missing. Thirdly, information bias from participants and data collectors may have affected the quality of data.

5. Conclusion

The results of this study provide valuable insight into the burden and management of Chest injury in Tanzania hospitals. It points to the need of establishing management guidelines for chest trauma in both pre-hospital and in-hospital setting. Since most of the chest trauma cases are due to Road traffic crashes, there is an urgent need of road traffic crash preventive measures to help reduce the frequency of chest injury in our population. Public awareness campaigns concerning road safety rules are needed as well as roads improvement.

What Is Known about This Topic?

- Accidents represent a significant proportional of non-communicable disease in Tanzania.
- Majority are due to road traffic crashes.
- Chest injury is among the common injuries sustained by the victims.

What This Study Adds

- This study provides valuable insight into the burden and management of Chest injury in Tanzania hospitals.
- It also points to the need of establishing management guidelines for chest trauma in both pre-hospital and in-hospital settings.

Authors' Contributions

Janeth Stanslaus Masuma, Respicious Lwezimula Boniface and Edwin Rwebugisa Lugazia conceived and designed the study. Janeth Stanslaus Masuma undertook the data collection and statistical analysis and wrote the first draft of the manuscript. All authors contributed to intellectual content and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sharma, P.P., Jhanwar, A., Sharma, D. and Sharma, S. (2016) Blunt Trauma Chest: Our Experience at Rural Tertiary Care Centre. *International Surgery Journal*, **3**, 261-265. https://doi.org/10.18203/2349-2902.isj20160239

[2] Miller, D.L. and Mansour, K.A. (2007) Blunt Traumatic Chest Injuries. *Thoracic Surgery Clinics*, **17**, 57-61. https://doi.org/10.1016/j.thorsurg.2007.03.017

[3] Okugbo, S.U., Okoro, E. and Irhibogbe, P.E. (2012) Functional Concepts in the Management of Simple Chest Injuries. *Journal of West African College of Surgeons*, **2**, 74-84.

[4] Søreide, K. (2009) Epidemiology of Major Trauma. *British Journal of Surgery*, **96**, 697-698. https://doi.org/10.1002/bjs.6643

[5] Taché, S., Mbembati, N., Marshall, N., Tendick, F., Mkony, C. and O'Sullivan, P. (2009) Addressing Gaps in Surgical Skills Training by Means of Low-Cost Simulation at Muhimbili University in Tanzania. *Human Resources for Health*, **7**, Article No. 64. https://doi.org/10.1186/1478-4491-7-64

[6] Lema, M.K., Chalya, P.L., Mabula, J.B. and Mahalu, W. (2011) Pattern and Outcome of Chest Injuries at Bugando Medical Centre in Northwestern Tanzania. *Journal of Cardiothoracic Surgery*, **6**, Article No. 7. https://doi.org/10.1186/1749-8090-6-7

[7] Frimpong-Boateng, K. and Amoati, A.B.G. (2000) Chest Injuries in Ghana. *West African Journal of Medicine*, **19**, 175.

[8] Inci, I., Ozçelik, I., Tacyildiz, O., Nizam, N., Eren, G. and Ozen, D.B. (1998) Penetrating Chest Injuries: Unusually High Incidence of High Velocity Gunshot Wounds in Civilian Practice. *World Journal of Surgery*, **22**, 438-442. https://doi.org/10.1007/s002689900412

[9] Boniface, R., Museru, L., Munthali, V. and Lett, R. (2013) Injury Experience in Tanzania—Need for Intervention. *The East African Medical Journal*, **90**, 171-179.

[10] Boniface, R., Museru, L., Kiloloma, O. and Munthali, V. (2016) Factors associated with road traffic injuries in Tanzania. *Pan African Medical Journal*, **23**, Article No 46. https://doi.org/10.11604/pamj.2016.23.46.7487

[11] Galukande, M., Jombwe, J., Fualal, J. and Gakwaya, A. (2009) Boda-Boda Injuries a Health Problem and a Burden of Disease in Uganda: A Tertiary Hospital Survey. *East and Central African Journal of Surgery*, **14**, 33-37.

[12] Saidi, H.S. and Nyaikamo, J. (2002) Gunshot Injuries as Seen at Agakhan Hospital Kenya. *East African Medical Journal*, **79**, 188-192. https://doi.org/10.4314/eamj.v79i4.8876

[13] Museru, L.M., Mcharo, C.N. and Leshabari, M.T. (2002) Road Traffic Accident in Tanzania: A Ten-Year Epidemiological Appraisal. *East and Central African Journal of Surgery*, **7**, 23-26.

[14] Muyembe, V.M. and Suleman, N. (1998) Head injuries at a Provincial General Hospital in Kenya. *East African Medical Journal*, **75**, 364-369.

[15] World Health Organization (2011) Motorcycle-Related Road Traffic Crashes in Kenya: Facts and Figures. https://www.who.int/violence_injury_prevention/road_traffic/countrywork/factsheet_kenya.pdf

[16] World Health Organization (2004) World Report on Road Traffic Injury Prevention. World Health Organization, Geneva. https://www.who.int/publications/i/item/world-report-on-road-traffic-injury-prevention

[17] Mwesigwa, M.M., Bitariho, D. and Twesigye., D. (2016) Patterns and Short-Term Outcomes of Chest Injuries at Mbarara Regional Referral Hospital in Uganda. *East and Central African Journal of Surgery*, **21**, 28-35. https://doi.org/10.4314/ecajs.v21i3.6

[18] Ali, N. and Gali, B.M. (2004) Pattern and Management of Chest Injury in Maiduguri, Nigeria. *Annals of African Medicine*, **13**, 181-184.

[19] Maxwell, R.A., Campbell, D.J., Fabian, T.C., Croce, M.A., Luchette, F.A., Kerwin, A.J., *et al.* (2004) Use of Presumptive Antibiotics Following Tube Thoracostomy for Traumatic Haemopneumothorax in the Prevention of Empyema and Pneumonia—A Multi-Center Trial. *Journal of Trauma*, **57**, 742-748. https://doi.org/10.1097/01.TA.0000147481.42186.42

[20] Masaga, F.A. and Mchembe, M. (2010) The Pattern and Management of Chest trauma at Muhimbili National Hospital, Dar es Salaam. *East and Central African Journal of Surgery*, **15**, 124-129.

[21] Mohan, A., Singh, G. and Kohli, A. (2006) Chest Trauma in Jammu Region an Institutional Study. *Indian Journal of Thoracic and Cardiovascular Surgery*, **22**, 219-222. https://doi.org/10.1007/s12055-006-0006-1

[22] Otieno, T., Woodfield, J.C., Bird, P. and Hill, A.G. (2004) Trauma in Rural Kenya. *Injury*, **35**, 1228-1233. https://doi.org/10.1016/j.injury.2004.03.013

[23] Saeed, A.Y., Hamza, A.A. and Ismail, O.M. (2015) Pattern and Management Outcome of Chest Injuries in Omdurman Teaching Hospital Sudan. *Global Journal of Medical Research*, **15**, 5-9.

[24] Bastos, R., Baisden, C.E., Harker, L. and Calhoon, J.H. (2008) Penetrating Thoracic Trauma. *Seminars in Thoracic and Cardiovascular Surgery*, **20**, 19-25. https://doi.org/10.1053/j.semtcvs.2008.01.003

[25] Robison, P.D., Harman, P.K., Trinkle, J.K. and Grover, F.L. (1988) Management of penetrating lung injuries in civilian practice. *The Journal of Thoracic and Cardiovascular Surgery*, **95**, 184-190. https://doi.org/10.1016/S0022-5223(19)35353-X

[26] Unsworth, A., Curtis, K. and Asha, S.E. (2015) Treatments for Blunt Chest Trauma and Their Impact on Patient Outcomes and Health Service Delivery. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **23**, Article No. 17. https://doi.org/10.1186/s13049-015-0091-5

[27] Ekpe, E.E. and Eyo, C. (2014) Determinants of Mortality in Chest Trauma Patients. *Nigerian Journal of Surgery*, **20**, 30-34.

[28] Chiumello, D., Coppola, S., Froio, S., Gregoretti, C. and Consonni, D. (2013) Non-invasive ventilation in chest trauma: Systematic review and meta-analysis. *Intensive Care Medicine*, **39**, 1171-1180. https://doi.org/10.1007/s00134-013-2901-4

[29] Kallet, R.H. (2004) Evidence-Based Management of Acute Lung Injury and Acute Respiratory Distress Syndrome. *Respiratory Care*, **49**, 793-809.

Appendix: Questionnaire

1) General information
a) Patient's file number ……
b) Gender
Male □ Female □
c) Age ……
d) Marital status ……
e) Education level …….
f) Time of injury …….
g) Time at admission …….
h) Time at management ……
2) Vital signs at admission
a) Pulse rate …….
b) Respiratory rate …….
c) Blood pressure……..
d) Spo2…….
3) Type of injury
Blunt □ Penetrating □
4) Mode of injury
a) Road traffic accidents
b) Fall from a height
c) assault
d) compression by heavy objects
e) blast
f) Others ……..
5) which part of the body is injured
a) head
b) Chest
c) Extremity
d) Abdomen
e) Pelvis
f) others……
6) Any preexisting comorbid conditions?
Yes-specify; Cardiac disease……
Respiratory disease…….
Liver disease……
Cancer……
Neurological disease……...
No
7) Screening for chest injury
a) Any chest pain or difficulty in breathing?
If yes, proceed to question 8
If no, end here

8) Findings on chest examination
Inspection…….
Palpation…….
Percussion……
Ascultation……
9) Investigations done
a) ABG
Yes □, Results …….
No □
b) CXR
c) Chest USS
d) Chest CT-scan
10) Pattern of chest injury
a) pneumothorax
b) hemothorax
c) pneumohemothorax
d) lung contusion
e) rib fracture
f) clavicle fracture
g) chest wall contusion
h) others
specify ……
11) Chest involvement
a) Unilateral…….
b) Bilateral…….
12) AIS_{thorax}
a) 1
b) 2
c) 3
d) 4
e) 5
f) 6
13) Options used for analgesia:
a) opioids
b) non opioids
c) a and b
d) multimodal
Assessment of adequacy of analgesia
a) verbal analog scale
b) visual analog scale
c) others; ….
14) Ventilation modes;
a) Invasive Ventilation……
b) Noninvasive ventilation……

If Invasive Ventilation, what is the length of mechanical ventilation (days)……..

Vital signs after ventilation

a) Spo2……

b) ABG……

c) RR…….

15) Any procedure/surgery done;

a) Thoracostomy

b) Thoracotomy

c) Laparotomy

d) Others…….

16) Any other treatment offered…….

17) Length of hospital stay……

18) Outcome

a) Discharged……

b) Died……..

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Usefulness of a Simple Protein-Energy Wasting Score for Predicting Hospitalization in Maintenance Hemodialysis Patients: A Prospective Cohort Study

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Abstract

Background: Malnutrition is a strong predictor of prognosis in maintenance hemodialysis patients (MHD). We previously proposed a new and simple protein-energy wasting (PEW) score that appears to be useful for assessing the risk of mortality in patients on MHD. **Objectives:** In the present study, we evaluated the reliability of this PEW score as a predictor of hospitalization in Japanese patients on MHD. **Methods:** In this single-center, prospective cohort study conducted in Japan, PEW score was calculated for 180 MHD patients. PEW score ranged from 0 (best: S1) to 4 (worst: S4) and was calculated based on nutritional indicators including serum albumin, body mass index, serum creatinine level, and protein intake. The outcome was the number of hospitalizations during the 2-year study period. **Results:** Thirty-six patients were hospitalized during the study period. Kaplan-Meier curves showed there were fewer hospitalizations in the group with a PEW score of 0/1 than in the group with a score of 3/4. Multivariate analysis revealed a hazard ratio for hospitalization of 3.109 for S3/4 versus S0, 2.777 for S3/4 versus S1, and 2.048 for S3/4 versus S2. **Conclusion:** The new and simple PEW score is a useful predictor of hospitalization in MHD patients and is also useful for identifying subgroups of MHD patients with a high risk of mortality.

Keywords

Protein-Energy Wasting, Hemodialysis, Hospitalization, Simple Score

1. Introduction

Patients on maintenance hemodialysis (MHD) have various nutritional disord-

ers due to the stepwise loss of body proteins and metabolic disorders [1]. Because malnutrition is a strong predictor of mortality in MHD patients, assessing their nutritional status is essential in managing these patients [2]. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) presented the concept of protein energy wasting (PEW) and proposed diagnostic criteria for PEW in MHD patients [3]. However, the proposed approach lacks versatility because it is difficult to assess the reduced muscle mass. To address this issue, a new and simplified scoring method using serum creatinine adjusted for body surface area (SCr/BSA) was proposed in 2014 [4].

Currently, there is no single gold standard marker for clinically evaluating nutritional status in MHD patients that are not affected by confounding factors and that can be measured by a method that is both simple and reproducible. Therefore, PEW has conventionally been evaluated based on the assessment of various factors. We previously proposed a new and simple PEW score that appears to be useful for assessing the risk of mortality in patients on MHD [5]. In the present study, we aimed to demonstrate the usefulness of this simple PEW score as a predictor of hospitalization in MHD patients.

2. Methods

2.1. Patients and Protocol

This was a single-center, prospective cohort study conducted over 24 months in Japan from June 1, 2017, to June 30, 2019, at Shinjuku Ishikawa Clinic. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Ishikawa Clinic (No. 2-01-2017). All subjects gave informed consent to participate.

This study enrolled MHD patients who had been undergoing hemodialysis (HD) via an arteriovenous fistula (AVF) for at least 6 months at Shinjuku Ishikawa Clinic. Exclusion criteria were malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, and other severe illness.

All patients received HD 3 times a week. Blood pressure was measured in the recumbent position in a resting state, and the mean blood pressure during the 1-month period prior to enrollment was used for the analysis. The dry weight was targeted so as to achieve a normotensive edema-free state. Diabetes mellitus was defined as fasting blood glucose of ≥126 mg/dL, hemoglobin A1c (HbA1c) of ≥6.5, or a history of medication with an oral hypoglycemic agent(s).

2.2. Laboratory and Nutritional Parameters

Blood sampling was performed before starting an HD session after overnight fasting. Blood urea nitrogen and serum creatinine, albumin, and C-reactive protein (CRP) were measured using an autoanalyzer (Hitachi Co., Tokyo, Japan). Body mass index (BMI) was calculated by dividing body weight in kilograms by height squared in meters. Urea kinetics was assessed by measuring the blood-based dialysis parameter, Kt/V [6], and the mean value of three measurements

obtained during each of the 3 months before the start of the study was used in the analysis.

PEW score was determined by grading one selected item in each of four categories, as previously described [5]: 1) serum albumin, 2) BMI, 3) predialysis SCr/BSA, and 4) normalized protein catabolic rate (nPCR). The threshold values used were serum albumin < 3.8 g/dL, BMI < 23 kg/m^2, SCr/BSA < 659 mmol/L/m^2, and nPCR < 0.8 g/kg/day. nPCR was used as an indirect indicator of protein intake and was calculated using a formula previously reported [7]. BSA was estimated using the Du Bois formula [8]. A threshold value of 659 mmol/L/m^2 for the SCr/BSA variable was selected based on the results of a receiver operating characteristics (ROC) curve analysis (**Figure 1**).

2.3. Study Outcome

Data for endpoints were obtained from hospital charts. The primary endpoint of the study was hospitalization. The following hospitalization data were collected: 1) date of hospitalization and discharge, 2) diagnosis, and 3) treatment. This study was a prospective study and the sample size was dependent on the number of HD patients eligible for enrollment in this study.

2.4. Statistical Analysis

Nonparametric values were expressed as median values and compared using the Kruskal-Wallis test. Categorical values were expressed as percentages and compared using Fisher's exact test. In univariate logistic regression, we determined variables with a *P*-value of <0.10, in addition to sex, presence of diabetes, CRP, and Kt/V. Hospitalization was analyzed based on the Kaplan-Meier curve. A log-rank test was used to compare the hospitalization rates of two groups. A multivariate Cox proportional hazard model with adjustment for multivariate factors was used to evaluate risk of hospitalization. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS version 9.2 software program (SAS Institute Inc., Cary, NC) for Windows personal computers. There were no missing data or loss to follow-up in this study.

3. Results

A total of 180 patients on stable HD maintained with a bicarbonate dialysate were enrolled in the study. The baseline characteristics of the participants classified using the PEW score are shown in **Table 1**. The study cohort consisted of 38 women and 142 men (mean age 61 years; mean dialysis vintage 10 years; mean BMI 21.8). The underlying kidney diseases were chronic glomerulonephritis (74 patients), diabetic kidney disease (62 patients), glomerulosclerosis (32 patients), and other (12 patients). None had any residual renal function (urine volume < 100 mL). Mean dialysis dose was 1.49 for a single-pool Kt/V, and mean protein intake was 1.12 g/kg/day. Of the 180 patients, 102 (56.7%) had moderate or se-

vere wasting. Data for all participants were available for analysis during the follow-up period. There were no missing data in this study.

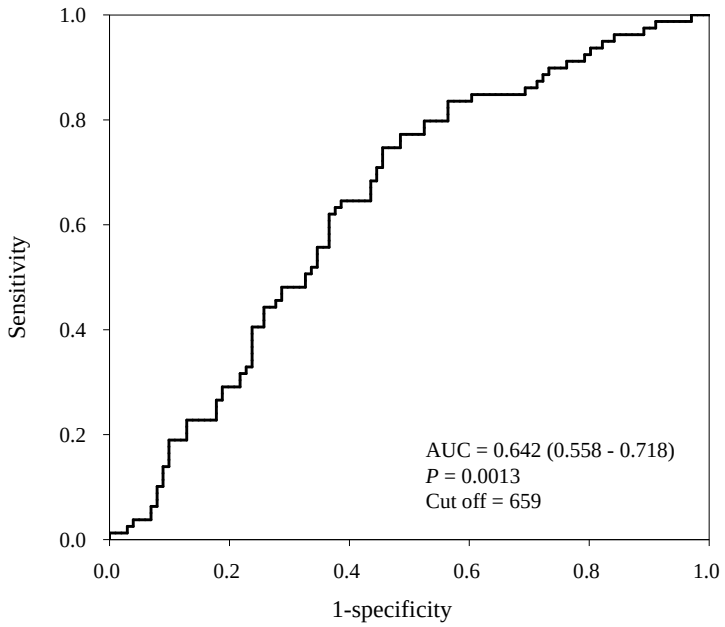

Figure 1. Receiver operating characteristic curve analysis to determine the optimal cut-off value of serum creatinine adjusted for body surface area for detecting hospitalization rate. Abbreviation: AUC, area under the curve.

Table 1. Baseline characteristics according to the protein-energy wasting score.

		Score 0	Score 1	Score 2	Score 3 - 4
Clinical and laboratory parameters	All	Normal nutritional status	Slight wasting	Moderate wasting	Severe wasting
Number of patients	180	18	60	65	37
Age (years)	61 (51 - 69)	50 (45 - 57)	55 (48 - 65)	61 (53 - 70)**	73 (66 - 80)*
Male (%)	142 (78.9)	16 (88.9)	52 (86.7)	53 (81.5)	21 (56.8)
Dialysis vintage (years)	10 (4 - 17)	10 (7 - 14)	10 (3 - 18)	13 (5 - 19)	9 (4 - 17)
BMI (kg/m^2)	21.8 (19.9 - 24.7)	26.4 (24.1 - 27.2)	21.9 (20.1 - 24.9)*	21.6 (20 - 24.5)*	20.4 (18.8 - 21.7)*
Kt/V	1.49 (1.36 - 1.61)	1.36 (1.24 - 1.56)	1.46 (1.36 - 1.58)	1.51 (1.34 - 1.61)	1.60 (1.40 - 1.78)**
nPCR (g protein/kg/day)	1.12 (0.97 - 1.27)	1.05 (0.97 - 1.23)	1.15 (0.99 - 1.35)	1.13 (0.96 - 1.29)	1.07 (0.88 - 1.20)
Hb (g/dL)	11.2 (10.8 - 11.7)	11.4 (10.9 - 12.0)	11.3 (10.9 - 11.7)	11.1 (10.8 - 11.6)	11 (10.2 - 11.8)
Serum albumin (g/dL)	3.8 (3.5 - 4.0)	4.0 (3.9 - 4.1)	3.9 (3.8 - 4.1)	3.7 (3.5 - 3.8)*	3.5 (3.4 - 3.6)*
Pre-albumin (mg/dL)	35.1 (29.4 - 40.9)	41.2 (37.9 - 51.2)	38.6 (34.2 - 42.3)	33.9 (29.5 - 39.1)*	27.8 (23.15 - 32.6)*
Creatinine/BSA (μmol/L/m^2)	635.8 (542.6 - 732.9)	780.2 (688.7 - 816.0)	709.7 (604.4 - 774.5)**	604.6 (528.2 - 688.4)*	556.6 (488.7 - 601.7)*
C-reactive protein (mg/dL)	0.10 (0.05 - 0.27)	0.13 (0.05 - 0.21)	0.07 (0.05 - 0.20)	0.08 (0.05 - 0.27)	0.21 (0.05 - 0.67)
Total cholesterol (mg/dL)	153 (133 - 169)	159 (140 - 181)	157 (140 - 173)	152 (135 - 167)	147 (127 - 164)
HDL cholesterol (mg/dL)	45 (36 - 54)	40 (33 - 50)	49 (40 - 60)	44 (35 - 53)	44 (36 - 50)
Triglyceride (mg/dL)	93 (62 - 151)	158 (135 - 182)	99 (76 - 146)**	86 (57 - 141)**	81 (59 - 121)**

Abbreviations: BMI, body mass index; Kt/V, blood-based dialysis parameter; nPCR, normalized protein catabolic rate; HDL, high-density lipoprotein; BSA, body surface area. *$P < 0.001$ versus score 0; **$P < 0.05$ versus score 0.

There were 168 hospitalizations during the 24-month follow-up period. The most common cause of hospitalization was pneumonia. Kaplan-Meier curve analysis revealed that the hospitalization rate was lower in the group with a PEW score of 0 (S0) than in the group with a high PEW score (S2-4; Figure 2). Table 2 shows predictors of hospitalization in the MHD patients. The HRs for hospitalization in the severe wasting group (S3/4) relative to the normal nutritional status group (S0), slight wasting group (S1) and moderate wasting group (S2) were 3.109, 2.774, and 2.048, respectively (Table 2).

Table 2. Predictive factors of hospitalization in patients on maintenance hemodialysis as determined by Cox proportional hazard models.

Patient characteristics and PEW score	HR	95% CI	*P*-value
Sex (male/female)	3.317	1.522 - 7.629	0.0022
Diabetes	2.252	1.354 - 3.777	0.0018
Myocardial infarction	1.309	0.492 - 2.909	0.5586
Peripheral vascular disease	1.709	0.402 - 4.952	0.4185
Stroke	1.636	0.907 - 2.821	0.0992
Dialysis vintage	0.998	0.967 - 1.028	0.8760
C-reactive protein	1.138	0.914 - 1.317	0.1391
Kt/V	4.795	1.342 - 16.940	0.0154
Score 3 - 4 versus 0	3.109	1.220 - 9.551	0.0160
Score 3 - 4 versus 1	2.774	1.423 - 5.439	0.0029
Score 3 - 4 versus 2	2.048	1.141 - 3.624	0.0169

Abbreviations: PEW score, protein-energy wasting score; HR, hazards ratio; CI, confidence interval; Kt/V, blood-based dialysis parameter.

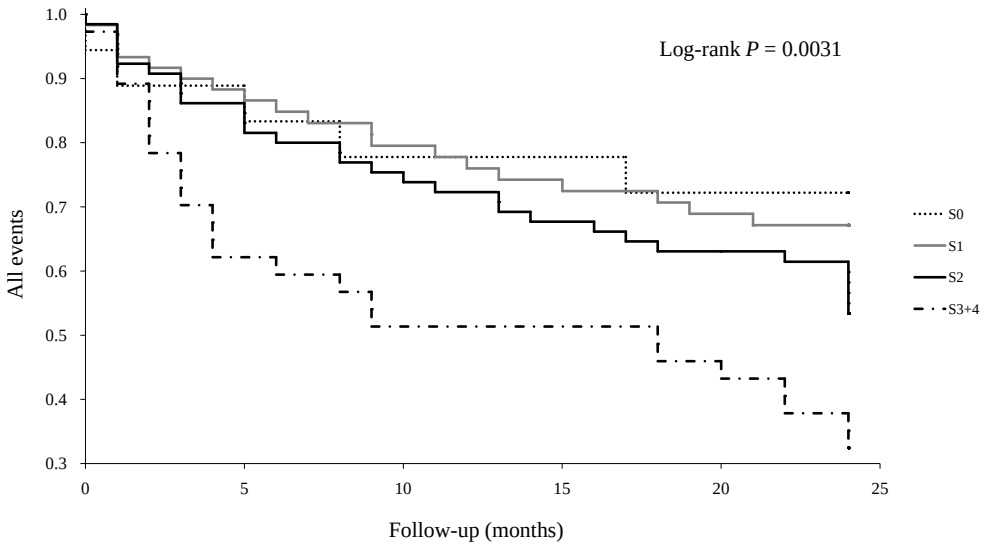

Figure 2. Kaplan-Meyer curve for hospitalization according to the protein-energy wasting score. S0 had a normal nutritional status, S1 had slight wasting, S2 had moderate wasting, and S3-4 had severe wasting.

4. Discussion

We evaluated the usefulness of a simple PEW score calculated from readily available clinical parameters and demonstrated its utility as a predictor of the risk of hospitalization in MHD patients. Although impaired nutritional status is frequently reported in MHD patients, there is no single nutritional parameter that can predict PEW. We hope to improve outcomes in MHD patients by using simple nutritional markers to evaluate their nutritional status.

Hypoalbuminemia is a strong predictor of mortality in MHD patients. Kalantar-Zadeh *et al.* showed that a serum albumin level of <3.8 g/dL in MHD patients was correlated with increased mortality from cardiovascular disease, independent of demographic, clinical and hematological data [9]. Also, Malfra *et al.* demonstrated that serum albumin level of <3.7 g/dL was a strong predictor of mortality in HD patients [10]. A 10-year cohort study reported increased risk of mortality in HD patients with a serum albumin level of ≤3.8 g/dl [11]. However, Friedman and Fadem [12] recently showed that the serum albumin level should be used cautiously as a nutritional marker in dialysis patients, because hypoalbuminemia could arise from both malnutrition and inflammation.

A lower prevalence of inflammation has been reported in HD patients in Asian countries, including Japan and Korea, and this lower prevalence may be associated with genetic factors and cultural habits, such as dietary factors [13] [14]. The prevalence of obesity in MHD patients appears to be paradoxically associated with a higher survival rate [15] [16]. Mortality in Asian-American HD patients is reported to be lower than that in Caucasian HD patients. In fact, Asian-Americans have a significantly lower BMI [17]. The ISRNM has proposed a BMI of ≤23 as a diagnostic criterion for PEW in patients with chronic kidney disease (CKD) patients [3], but has not recommended its use in South Asian CKD patients [5].

nPCR reflects dietary protein intake [18], and it was reported to be an independent predictor of mortality in MHD patients [19]. A study by Chandna *et al.* showed a substantial decrease in nPCR among CKD patients at 3 months before the start of dialysis [20]. The Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) clinical practice guidelines recommend a daily protein intake of 1.2 - 1.3 g/kg/day for MHD patients [21]. Lukowsky *et al.* reported that patients with nPCR decreased by ≥0.2 within 3 months before the start of dialysis have an increased risk of death [22].

No single parameter allows for comprehensive and conclusive assessment of nutritional status in HD patients. Therefore, collective evaluation of multiple nutritional markers is recommended by the K/DOQI guidelines [21]. A recent expert panel has suggested the use of markers from four different categories (blood biochemistry, BMI, muscle mass, and dietary intake) for the clinical diagnosis of PEW [3]. Three out of these four categories should be selected, including at least one biochemical factor, to satisfy this diagnosis. However, to our knowledge, these combinations have not yet been tested for the assessment of nutritional status in MHD patients.

Moreau-Gaudry *et al.* [4] reported a simple PEW scoring method that includes one parameter from each of the following major groups proposed for nutritional intervention: 1) biological parameters, 2) body composition, 3) muscle mass, and 4) nutrient intake. It seems important to add hematological data (e.g., serum albumin and serum creatinine) and other clinical information (e.g., BMI). Muscle mass represents an important body feature strongly associated with survival, but because assessment of muscle mass is difficult, predialysis SCr/BSA was used for the assessment. SCr/BSA values differ between Western and Asian subjects, and may vary depending on creatinine uptake and metabolism. This is why serum creatinine is not used routinely. In fact, SCr/BSA shows a better fit to the Cox model than serum albumin. Eventually, we decided to include protein intake, estimated by the nPCR, as information on nutrient intake in the score. This value is also listed in the recent international recommendations and can be easily calculated using dialysis generator software. The inclusion of SCr/BSA in our model improved the prediction of hospitalization compared with the use of albumin alone.

Our study has several limitations. First, because some participants had comorbid conditions, the way in which the study population was enrolled may have introduced selection bias and may have failed to gather a representative sample of the general Japanese population. Second, it should be noted that the score itself was not better than the four parameters included in the model as separate variables [4]. However, this result was not unexpected, because the information given by the score depends on the variables included in the score. We believe that this score is of interest because it would encourage dialysis staff to pay more attention to all of these variables. The PEW score can be calculated within minutes at the bedside and requires no additional preparation or expense. The final patient classification we obtained corresponds well to a publication on the prevalence of nutritional disorders in MHD patients, which reports that moderate and severe nutritional disorders are found in 37% and 19% of HD patients, respectively [23].

5. Conclusion

This simple-to-calculate nutritional score is useful for the identification of PEW in MHD patients in routine clinical practice. Further studies are needed to establish the PEW score in Asian populations because of differences in body composition and clinical practice.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Kalantar-Zadeh, K., Ikizler, T.A., Block, G., Avram, M.M. and Kopple, J.D. (2003) Malnutrition-Inflammation Complex in Dialysis Patients: Causes and Consequences. *American Journal of Kidney Diseases*, **42**, 864-881. https://doi.org/10.1016/j.ajkd.2003.07.016

[2] Lopes, A.A., Bragg-Gresham, J.L., Elder, S.J., Ginsberg, N., Goodkin, D.A., Pifer, T., Lameire, N., Marshall, M.R., Asano, Y., Akizawa, T., Pisoni, R.L., Young, E.W. and Port, F.K. (2010) Independent and Joint Associations of Nutritional Status Indicators with Mortality Risk among Chronic Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Journal of Renal Nutrition*, **20**, 224-234. https://doi.org/10.1053/j.jrn.2009.10.002

[3] Fouque, D., Kalantar-Zadeh, K., Kopple, J., Cano, N., Chauveau, P., Cuppari, L., Franch, H., Guamieri, G., Ikizler, T.A., Kaysen, G., Lindholm, B., Massy, Z., Mitch, W., Pineda, E., Stenvinkel, P., Trevino-Becerra, A. and Wanner, C. (2008) A Proposed Nomenclature and Diagnostic Criteria for Protein-Energy Was Ting in Acute and Chronic Kidney Disease. *Kidney International*, **73**, 391-398. https://doi.org/10.1038/sj.ki.5002585

[4] Moreau-Gaudry, X., Jean, G., Genet, L., Lataillade, D., Legrand, E., Kuentz, F. and Fouque, D. (2014) A Simple Protein-Energy Wasting Score Predicts Survival in Maintenance Hemodialysis Patients. *Journal of Renal Nutrition*, **24**, 395-400. https://doi.org/10.1053/j.jrn.2014.06.008

[5] Kobayashi, S., Suzuki, K., Ueda, M., Tanaka, Y. and Nitta, K. (2015) A Simple Protein-Energy Wasting Score for Survival Prediction of Maintenance Hemodialysis Patients. *Renal Replacement Therapy*, **1**, Article No. 1. https://doi.org/10.1186/s41100-015-0012-0

[6] Daugirdas, J.T. (1993) Second Generation Logarithmic Estimates of Single-Pool Variable Volume Kt/V: An Analysis of Error. *Journal of American Society of Nephrology*, **4**, 1205-1213. https://doi.org/10.1681/ASN.V451205

[7] Shinzato, T., Nakai, S., Fujita, Y., Takai, I., Morita, H., Nakane, K. and Maeda, K. (1994) Determination of Kt/V and Protein Catabolic Rate Using Pre- and Postdialysis Blood Urea Nitrogen Concentrations. *Nephron*, **67**, 280-290. https://doi.org/10.1159/000187980

[8] Du Bois, D. and Du Bois, E.F. (1989) A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known. *Nutrition*, **5**, 303-311.

[9] Kalantar-Zadeh, K., Kilpatrick, R.D., Kuwae, N., McAllister, C.J., Alcom, H.Jr., Kopple, J.D. and Greenland, S. (2005) Revising Mortality Predictability of Serum Albumin in the Dialysis Population: Time Dependency, Longitudinal Changes and Population-Attributable Fraction. *Nephrology Dialysis Transplantation*, **9**, 1880-1888. https://doi.org/10.1093/ndt/gfh941

[10] Mafra, D., Farage, N.E., Azevedo, D.L., Viana, G.G., Mattos, J.P., Velarde, L.G.C. and Fouque, D. (2007) Impact of Serum Albumin and Body-Mass Index on Survival in Hemodialysis Patients. *International Urology and Nephrology*, **39**, 619-624. https://doi.org/10.1007/s11255-007-9201-2

[11] Kato, A., Takita, T., Furuhashi, M., Maruyama, Y. and Hishida, A. (2010) Comparison of Serum Albumin, C-Reactive Protein and Carotid Atherosclerosis as Predictors of 10-Year Mortality in Hemodialysis Patients. *Hemodialysis International*, **14**, 226-232. https://doi.org/10.1111/j.1542-4758.2009.00432.x

[12] Friedman, A.N. and Fadem, S.Z. (2010) Reassessment of Albumin as a Nutritional Marker in Kidney Disease. *Journal of American Society of Nephrology*, **21**, 223-230.

https://doi.org/10.1681/ASN.2009020213

[13] Oldroyd, J.C., Heald, A., Bansal, N., Vyas, A., Siddals, K., Gibson, M., Clayton, P. and Cruickshamk, J.K. (2009) Inflammatory Markers and Growth in South Asian and European Origin Infants in Britain: The Manchester Children's Growth and Vascular Health Study. *Atherosclerosis*, **207**, 227-231. https://doi.org/10.1016/j.atherosclerosis.2009.03.045

[14] Coe, C.L., Love, G.D., Karasawa, M., Kawakami, N., Kitayama, S., Markus, H.R., Tracy, R.P. and Ryff, C.D. (2011) Population Differences in Proinflammatory Biology: Japanese Have Healthier Profiles than Americans. *Brain Behavior and Immunology*, **25**, 494-502. https://doi.org/10.1016/j.bbi.2010.11.013

[15] Kalantar-Zadeh, K., Kopple, J.D., Kilpatrick, R.D., McAllister, C.J., Shinaberger, C.S., Gjertson, D.W. and Greenland, S. (2005) Associations of Morbid Obesity and Weight Change over Time with Cardiovascular Survival in Hemodialysis Patients. *American Journal of Kidney Dis*eases, **46**, 489-500. https://doi.org/10.1053/j.ajkd.2005.05.020

[16] Kalantar-Zadeh, K., Kuwae, N., Wu, D.Y., Shantouf, R.S., Fouque, D., Anker, S.D., Block, F. and Kopple, J.D. (2006) Associations of Body Fat and Its Changes over Time with Quality of Life and Prospective Mortality in Hemodialysis Patients. *American Journal of Clinical Nutri*tion, **83**, 202-210. https://doi.org/10.1093/ajcn/83.2.202

[17] Wong, J.S., Port, F.K., Hulbert-Shearon, T.E., Carroll, C.E., Wolfe, R.A., Agodoa, L.Y. and Daugirdas, J.T. (1999) Survival Advantage in Asian American End-Stage Renal Disease Patients. *Kidney International*, **55**, 2515-2523. https://doi.org/10.1046/j.1523-1755.1999.00464.x

[18] Shinaberger, C.S., Kilpatrick, R.D., Regidor, D.L., McAllister, C.J., Greenland, S., Kopple, J.D. and Kalantar-Zadeh, K. (2006) Longitudinal Associations between Dietary Protein Intake and Survival in Hemodialysis Patients. *American Journal of Kidney Dis*eases, **48**, 37-49. https://doi.org/10.1053/j.ajkd.2006.03.049

[19] Mancini, A., Grandaliano, G., Magarelli, P. and Allegretti, A. (2003) Nutritional Status in Hemodialysis Patients and Bioimpedance Vector Analysis. *Journal of Renal Nutri*tion, **13**, 199-204. https://doi.org/10.1016/S1051-2276(03)00079-7

[20] Chandra, S.M., Kulinskaya, E. and Farrington, K. (2005) A Dramatic Reduction of Normalized Protein Catabolic Rate in the Course of Progressive Renal Insufficiency. *Nephrology Dialysis Transplantation*, **20**, 2130-2138. https://doi.org/10.1093/ndt/gfh940

[21] K/DOQI (200) National Kidney Foundation. Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *American Journal of Kidney Diseases*, **35**, S1-S140.

[22] Lukowsky, L.P., Khefets, L., Arah, O.A., Nissenson, A.R. and Kalantar-Zadeh, K. (2014) Nutritional Predictors of Early Mortality in Incident Hemodialysis Patients. *International Urology and Nephrol*ogy, **46**, 129-140. https://doi.org/10.1007/s11255-013-0459-2

[23] Dukkipati, R. and Kopple, J.D. (2009) Causes and Prevention of Protein-Energy Wasting in Chronic Renal Failure. *Seminars in Nephrology*, **29**, 39-49. https://doi.org/10.1016/j.semnephrol.2008.10.006

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Hyperuricemia in Hypertension and Chronic Kidney Disease: Risk Factors, Prevalence and Clinical Correlates: A Descriptive Comparative Study

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Abstract

Introduction: Uric acid is a product of purine metabolism and elevated serum concentration are very common in, and linked with hypertension and chronic kidney disease, conditions associated with heavy health burden and cardiovascular complications particularly in sub Sahara Africa. An assessment of factors relating hyperuricemia to hypertension and chronic kidney disease would therefore be necessary as way of mitigating the poor quality of life, morbidity and mortality associated with these diseases in low income nations. **Methods:** A single centre, descriptive comparative study in which the demographic, clinical and laboratory data of hypertensive and non-dialyzed chronic kidney disease (CKD) patients were analyzed. Serum biochemical parameters with uric acid, hematocrit and urine dip strip protein were assessed. Predictors of hyperuricemia were determined using multivariate analysis. **Results:** One hundred and thirty nine hypertensives and 69 CKD were studied. The mean age of the participants was 54.3 ± 11.7 years, hypertensives (52.9 ± 15.7 years) and CKD (57.3 ± 16.1 years). Both groups had more males, P = 0.8. Majority (78.3%) of the CKD cohorts had stage 4 or 5 (non-dialyzed) disease. The systolic and diastolic blood pressure, creatinine and uric acid were lower in hypertension than in CKD, P = 0.07, P = 0.05, P < 0.001 and P = 0.004 respectively. The hematocrit, albumin and GFR were

higher in HTN than CKD, P < 0.001, P < 0.001 and P < 0.001 respectively. The prevalence of hyperuricemia was 56.2%. The mean uric acid was 505.9 ± 23.6 mmol/L, 382 7 ± 10.5 mmol/L for hypertensive and 755.9 ± 14.8 mmol/L for CKD, P < 0.001. The prevalence of systolic HTN, proteinuria, hypoalbuminemia and anemia were 51%, 75%, 46% and 59%, and were higher in males. Hyperuricemia was related to advancing age, proteinuria, elevated creatinine, hypoalbuminemia, anemia and hypertriglyceridemia. Proteinuria (OR—4.66, 95% CI—2.42 - 9.65), elevated creatinine (OR—3.12, 95% CI—2.40 - 6.92), hypoalbuminemia (OR—2.92, 95% CI—1.83 - 5.78) and anemia (OR—4.01, 95% CI—3.78 - 7.99) independently predicted hyperuricemia. **Conclusion:** Hyperuricemia is commoner in CKD than hypertension and was higher in males and positively correlated with the blood pressure, proteinuria and creatinine, but negatively related to hematocrit, albumin and glomerular filtration rate. Independent predictors of hyperuricemia were proteinuria, elevated creatinine, hypoalbuminemia and anemia. Measures are needed to prevent and treat hyperuricemia to reduce the health burden associated with hypertension and CKD.

Keywords

Hyperuricemia, Hypertension, Chronic Kidney Disease, Anemia, Hypoalbuminemia, Inflammation, Atherosclerosis, Reactive Oxygen Specie

1. Introduction

Hyperuricemia has been identified as a risk factor for hypertension (HTN), and the occurrence and progression of chronic kidney disease (CKD) including cardiovascular events [1]. Hypertension and CKD have been on the increase worldwide with worsening socioeconomic burden, just as the prevalence of hyperuricemia in hypertension and CKD is reported to be on the increase leading to a faster progression of hypertension to CKD, and CKD progression to end stage kidney disease (ESRD) [2]. The prevalence CKD in sub-Sahara Africa (SSA) is about 13.9% and the prevalence of hyperuricemia in CKD in SSA is reported to be 15.2% - 67% [3] [4] [5].

Uric acid (UA) as a product of purine nucleotides catabolism, is known to be more commonly elevated in HTN and CKD than in health [2]. Common sources of UA include animal proteins and fructose containing diet and drinks [3]. Although a definitive causative relationship has not been established between hyperuricemia and HTN or CKD, the associations between hyperuricemia and HTN, and with CKD are reported to be mediated through chronic inflammatory changes with renal microvascular injury involving the endothelium induced by the activation of the renin angiotensin aldosterone system (RAAS) [6]. This occurs mostly in the intracellular and intravascular spaces and an end point of this inflammatory state is endothelial injury, release of vasoactive cytokines, atherosclerosis and increased cardiovascular risk profile [7]. Uric acid as a weak acid is

also reported to have strong anti-oxidant properties in the extracellular (EC) space [8].

Hyperuricemia is reported to mitigate the inflammatory injury associated with many chronic inflammatory and degenerative diseases like Alzheimers' disease, Parkinson's disease and chronic obstructive lung diseases (COPD) [9] [10] [11]. Nieto *et al.* [12] reported that in atherosclerotic patients, hyperuricemia induces a compensatory reduction in vascular oxidative damage with increased proximal tubular sodium absorption, as found in hyperinsulinemia. The world health organization (WHO) reported that over one billion people have hyperuricemia worldwide accounting for 13% of death and is implementing a preventive program aimed at reducing the global prevalence of hyperuricemia by 25% by the year 2025 [13]. Hyperuricemia is reported to be commoner in urban than rural communities and this has been attributed to the lifestyle pattern in urban settings associated with dietary indiscretion, particularly high intake of animal protein and fructose (sweetened) containing drinks [5].

Apart from uric acid stones, hyperuricemia is known to induce gout in addition to renal inflammation [9]. The occurrence of hyperuricemia from declining renal losses is often time, due to the inability of the compensatory increases in gastrointestinal losses to keep serum levels within normal [14]. Hyperuricemia has a synergistic effect on kidney function decline which could lead to a worsening metabolic acidosis (MA) and declining hematocrit, although the bimodal profile of serum albumin concentration (regarding increases as an inflammatory marker and reduction from increased losses, both prominent features of CKD) makes it difficult to draw outright conclusions, based only on its blood levels [15]. Considering the association between hyperuricemia and conditions like hypertension, CKD and cardiovascular disease, some authors have assessed the impact of uric acid lowering agents on renal and cardiovascular function [16] [17]. However, a generalized causal relationship is still being debated, it might still be a sound clinical verdict to assume the renal, cardiac and vascular toxicity of hyperuricemia, thereby, cautiously preventing it and its associated health burden.

Hyperuricemia is well reported locally and internationally, however, literature is scares concerning a comparative assessment of its associations with hypertension, and CKD, regarding determinants and clinical correlates. We hypothesize that hyperuricemia is common among hypertensives but more so in CKD. We compared hyperuricemiain hypertension and CKD.

2. Materials and Methods

This was a singer center hospital based descriptive, comparative study carried out at the Nephrology and Hypertension Clinic of Babcock University Teaching Hospital, Ilishan-Remo, Nigeria, from August 2019 to January 2021. Two hundred and eight (139 hypertensives and 69 non-dialyzed CKD) participants, sixteen years or older, attending the nephrology and hypertension clinic were consecutively recruited after obtaining informed consent. Chronic kidney disease

was defined according to the KDOQI 2012 criteria [18]. Participants were not taking uric acid lowering agents at the time of sample collection. All participants had a kidney ultrasound scan and participants with kidney length less than 9cm were classified as having CKD [19].

3. Exclusion Criteria

Patients with kidney graft, pelvic tumors, infections and HWCKD with proteinuria were excluded. Infections were ruled out by: the absence of fever (T < 37.4˚C) or leucocytes or nitrites on urine analysis and, with a normal ranged white cell count (WCC) and differentials from full blood count test. Hypertensives without CKD with any of the following conditions: diabetes, sickle cell anemia, liver disease, heart failure, proteinuria on urinalysis or kidney length < 9 cm on kidney ultrasound, other conditions that impacted negatively on kidney function, were excluded.

The sample size was calculated using the prevalence of hyperuricemia in a similar study [20].

Data was taken from history and patients' case notes and variables retrieved were age, gender, family history of hypertension and CKD, type and etiology of CKD.

Participants' height was taken without shoes, caps or head gear and weight on very light clothing using standardized scales and the body mass index (BMI) was calculated. The blood pressure (BP) was taken with a mercury sphygmomanometer (ACCOSON, England) with an appropriate standard cuff, after at least, 5 minutes rest.

Five milliliters of venous blood was collected from a peripheral vein into a Lithium heparin bottle for estimation of serum sodium, potassium, bicarbonate, chloride, urea, creatinine and uric acid. Serum biochemical analysis was determined using an autoanalyzer (Roche Diagnostics GmbH, Mannheim Germany). The creatinine based glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. About 1 milliliter of blood was also taken for determination of the hematocrit using a hematocrit centrifuge. An on-the-spot urinalysis was carried out on all participants' urine samples. Participants' fasting blood glucose (FBS) was determined using an Omron glucometer with glucose oxidase impregnated stripe.

4. Definitions

Hypeuricemia: Males > 0.42 mmol/L, Females > 0.36 mmol/L [20].

Hypertension: ≥140/90 mmHg [21].

Diabetes: Medical records confirming disease or history of use of antidiabetic drugs.

Dyslipidaemia: Total cholesterol ≥ 6.21 mmol/L.

Low-density lipoprotein cholesterol (LDL) > 4.14 mmol/L

High-density lipoprotein cholesterol (HDL) < 1.03 mmol/L

Triglycerides ≥ 1.69 mmol/L [22]

Anemia: Hematocrit < 33% [23]

Proteinuria: dip strip protein ≥ 1+ [24]

Hypoalbuminemia: serum albumin < 35 mg/dL [25]

eGFR (CKD-EPI)-ml/min/1.73m^2 [26]

Data analysis was carried out SSPS 22. Continuous variables are presented as mean with standard deviation and compared using student's t-test while categorical variables are presented as proportions and frequencies and compared using Chi-square or fisher's exact test. The P-value < 0.05 was considered statistically significant. After univariate analyses, variables with p < 0.025 were included as adjustment variables in multivariate analyses to determine variables that predicted hyperuricemia. Missing data where excluded from the analysis pairwise. This study was approved by the Babcock University Human Research Ethics Committee (NHREC/24/01/2018 and BUHREC501/19).

5. Results

Two hundred and eight participated (139 hypertensives and 69 CKD). The mean age of all participants was 54.3 ± 11.7 years, with hypertensives without CKD (52.9 ± 15.7 years) and CKD (57.3 ± 16.1 years) respectively. Males made up 64.9%, 64.0% and 66.7% of all participants, hypertensives and CKD respectively, P = 0.8. Three (4.3%) of the CKD cohort had stage 2 disease, 5 (7.2%) in stage 3a, 7 (10.1%) in stage 3b, 13 (18.8%) in stage 4 and 41 (59.4%) in stage 5 (non-dialytic). As participants advanced in age, the prevalence of hypertension and CKD increased, P = 0.13. The mean BMI was lower in HTN than in CKD, P = 0.08. The systolic and diastolic blood pressure, serum potassium, urea, creatinine and uric acid were lower in hypertension than in CKD, P = 0.07, P = 0.05, P < 0.001, P < 0.001, P < 0.001 and P = 0.004 respectively (**Table 1**). The serum sodium, bicarbonate, chloride, hematocrit, albumin and GFR were higher in HTN than in CKD, P < 0.001, P = 0.028, P = 0.005, P < 0.001, P < 0.001 and P < 0.001 respectively. The mean serum uric acid for study population was 505.9 ± 23.6 mmol/L. There was no statistical difference between the mean blood glucose of participants with hypertension and, with CKD, P = 0.7.

The mean uric acid was 505.9 ± 23.6 mmol/L, 382 7 ± 10.5 mmol/L in HWCKD and 755.9 ± 14.8 mmol/L for CKD, P < 0.001. The serum uric acid was higher in males and was positively correlated with the age, BMI, the systolic BP, level of proteinuria and serum creatinine, P < 0.001, P < 0.001, P = 0.001, P < 0.001 and P < 0.001 respectively, but was negatively correlated with serum bicarbonate, albumin, and hematocrit, P < 0.001, P < 0.001 and P < 0.001 respectively (**Table 2**). Derangements of serum biochemical and hematological parameters were associated with greater differences in the uric acid concentration between HWCKD and CKD.

The prevalence of hyperuricemia, systolic HTN, proteinuria, hypoalbuminemia and anemia in all participants were 56.3%, 51.0%, 75.0%, 46.2% and 59.1% respectively (**Table 3**), and were all higher in males than females.

Univariate analysis (**Table 4**) showed that advancing age, male gender, prote-

inuria, elevated creatinine, hypoalbuminemia, anemia and hypertriglyceridemia were associated with hyperuricemia. Multivariate analysis (Table 5) however showed only proteinuria (OR—4.66, 95% CI—2.42 - 9.65, P < 0.001), elevated creatinine (OR—3.12, 95% CI—2.40 - 6.92, P = 0.002), hypoalbuminemia (OR—2.92, 95% CI—1.83 - 5.78, P = 0.01) and anemia (OR—4.01, 95% CI—3.78 - 7.99, P = 0.001) independently predicted hyperuricemia.

Table 1. Sociodemographic, clinical and laboratory characteristics of participants.

Variables	Total N = 208 (%) Mean ± SD	Hypertension N = 139 (%) Mean ± SD	CKD N = 69 (%) Mean ± SD	P-value
Sex				
Males	135 (64.9)	89 (64.0)	46 (66.7)	0.8
Females	73 (35.1)	50 (36.0)	23 (33.3)	
Age, yrs				
Mean	54.3 ± 11.6	52.9 ± 15.7	57.3 ± 16.1	0.04
<65	99 (47.6)	68 (48.9)	31 (44.9)	0.05
>65	109 (52.4)	71 (51.1)	38 (55.1)	
BMI, kg/m^2				
<25.0	88 (47.1)	69 (49.6)	29 (42.0)	0.08
>25.0	110 (52.9)	70 (50.4)	40 (58.0)	
Systolic BP, mmHg				
<140	102 (51.0)	70 (50.4)	32 (46.4)	0.07
>140	106 (49.0)	69 (49.6)	37 (53.6)	
Diastolic BP, mmHg				
<90	96 (46.2)	65 (46.8)	31 (44.9)	0.05
>90	112 (53.8)	74 (53.2)	38 (55.1)	
Proteinuria, (>15 mg/dL)	156 (75.0)	91 (65.5)	65 (94.2)	<0.001
Sodium, mmol/L	134.5 ± 5.5	136.9 ± 5.2	132.8 ± 8.4	<0.001
Potassium, mmol/L	4.1 ± 1.0	3.9 ± 0.6	4.4 ± 1.02	<0.001
Chloride, mmol/L	99.8 ± 3.7	101.0 ± 8.7	97.5 ± 8.0	0.005
Bicarbonate, mmol/L	25.8 ±12.6	27.2 ± 16.3	23.0 ± 14.1	0.028
Calcium, mmol/L	2.3 ± 1.0	2.5 ± 1.2	2.0 ± 0.4	0.03
Phosphate, mmol/L	1.8 ± 0.6	1.6 ± 1.1	2.3 ± 1.4	0.002
Urea, mmol/L	14.8 ± 7.3	8.7 ± 3.0	26.9 ± 16.4	<0.001
Creatinine, umol/L	187.6 ± 43.1	143 ±.50.6	275 ±.57.0	<0.001
eGFR, ml/min	46.9 ± 4.9	69.6 ± 3.4	21.7 ± 5.8	<0.001
Uric acid, mmol/L	505.9 ± 23.6	382.7 ± 10.5	755.9 ± 14.8	<0.001
Hematocrit, %	34.1 ± 6.6	39.4 ± 6.8	25.9 ± 7.9	<0.001
RBG, mmol/L	118.8 ± 11.7	118.4 ± 14.3	111.9 ± 11.8	0.7
Albumin, mg/dL	39.3 ± 8.3	42.1 ± 8.6	33.7 ± 6.9	<0.001

CKD—chronic kidney disease, BMI—body mass index, BP—blood pressure, eGFR—estimated glomerular filtration ratio, RBG—random blood glucose.

Table 2. Comparison between the uric acid in hypertension and chronic kidney disease.

Variables	Total Uric acid mmol/L N = 208 (%) Mean ± SD	Hypertension Uric acid mmol/L N = 139 (%) Mean ± SD	CKD Uric acid mmol/L N = 69 (%) Mean ± SD	P-value
Mean	505.9 ± 23.6	382 7 ± 10.5	755.9 ± 14.8	<0.001
Sex				
Males	516. 8 ± 22.6	422.5 ± 21.5	825.9 ± 33.7	<0.001
Females	452.0 ± 84.8	329.4 ± 78.4	648.0 ± 91.8	0.001
Age, years				
<65.0	444.7 ± 5	308.0 ± 21.4	513.3 ± 23.6	0.05
>65.0	555.7 ± 33.2	466.2 ± 28.5	853.5 ± 33.7	<0.001
BMI, kg/m^2				
<25.0	496.3 ± 77.5	355.4 ± 36.8	612.5 ± 67.4	0.04
>25.0	513.1 ± 34.3	402.0 ± 67.7	824.5 ± 86.2	<0.001
Systolic BP, mmHg				
<140	473.4 ± 23.9	356.7 ± 18.6	727.2 ± 34.0	0.03
>140	528.8 ± 51.5	405.3 ± 23.6	793.0 ± 57.2	0.001
Proteinuria				
>15 mg/dL	557.3 ± 13.7	433.8 ± 23.6	782.6 ± 36.3	<0.001
<15 mg/dL	348.9 ± 9.9	283.8 ± 11.5	316.5 ± 10.6	0.05
Creatinine, umol/L				
<110	398.6 ± 18.2	323.7 ± 9.6	739.7 ± 24.2	<0.001
>110	585.4 ± 22.4	415 ± 31.4	769.5 ± 13.7	<0.001
Bicarbonate, mmol/L				
<22	558.3 ± 9.5	416 2 ± 22.5	802.1 ± 11.6	<0.001
>22	476.3 ± 8.8	369.4 ± 7.9	714.6 ± 10.9	0.04
Albumin, mg/dL				
<35	572.1 ± 10.4	446.3 ± 11.5	795.8 ± 14.5	<0.001
>35	458.7 ± 9.	351.8 ± 9.3	728.9 ± 9.9	<0.001
Hematocrit, %				
<33	532.2 ± 7.8	426.0 ± 8.3	867.2 ± 9.5	<0.001
>33	411.9 ± 7.5	331. 7 ± 11.6	601.4 ± 12.4	0.001

CKD—chronic kidney disease, BMI = body mass index, BP—blood pressure.

Table 3. Prevalence of hyperuricemia and its markers in the study population.

Variables	Total	Males	Females	P-value
	N = 208 (%)	N = 135 (%)	N = 73 (%)	
Hyperuricemia	117 (56.3)	86 (63.7)	31 (42.5)	0.08
Systolic hypertension	106 (51.0)	77 (57.0)	29 (39.7)	0.06
Proteinuria	156 (75.0)	114 (84.4)	42 (57.5)	0.04
Elevated creatinine	147 (70.7)	110 (81.5)	37 (50.7)	0.04
Hypoalbuminemia	96 (46.2)	69 (51.1)	27 (37.0)	0.16
Anemia	123 (59.1)	81 (60.0)	42 (57.3)	0.62
Low HDL	107 (51.4)	72 (53.3)	35 (47.9)	0.42
Elevated LDL	100 (48.1)	72 (53.3)	28 (38.4)	0.06
Hypertriglyceridemia	111 (53.4)	77 (57.0)	33 (45.2)	0.33

LDL—low density lipoprotein, HDL—high density lipoprotein.

Table 4. Univariate analysis of factors associated with hyperuricemia.

Variables	No Hyperuricemia	Hyperuricemia	P-value
	N = 91	N = 117	
Age, years (Mean ± SD)	33.9 ± 4.7	63.3 ± 8.5	<0.001
Sex	91	117	0.03
Males (n, %)	49 (36.3)	86 (63.7)	
Females (n, %)	42 (57.5)	31 (42.5)	
Hypertension (n, %)	74 (53.2)	65 (46.8)	0.001
CKD (n, %)	17 (24.6)	52 (75.4)	
Overweight/Obesity (n, %)	34 (37.4)	76 (65.0)	0.04
Proteinuria (n, %)	52 (57.1)	104 (88.9)	<0.001
Elevated creatinine, mean	162.6 ± 13.6	226.8 ± 21.3	<0.001
(range)	(92.7 - 184.6)	(118.7 - 357.9)	
(n, %)	36 (39.6)	111 (94.9)	
Hypoalbuminemia (n, %)	17 (18.7)	79 (67.5)	<0.001
Anemia (n, %)	31 (34.1)	92 (78.6)	<0.001
Low HDL (n, %)	34 (37.4)	73 (62.4)	0.07
Elevated LDL (n, %)	30 (33.0)	70 (59.8)	0.05
Hypertriglyceridemia	32 (35.2)	79 (67.5)	0.02

CKD—chronic kidney disease, HDL—high density lipoprotein, LDL—low density lipoprotein.

Table 5. Multivariate analysis of independent predictors of hyperuricemia.

Variables	OR	95% CI	P-value
Age	1.17	1.04 - 4.26	0.05
Proteinuria	4.66	2.42 - 9.65	<0.001
Elevated creatinine	3.12	2.40 - 6.92	0.002
Hypoalbuminemia	2.92	1.83 - 5.78	0.01
Anemia	4.01	3.78 - 7.99	0.001
Hypertriglycedemia	1.08	0.96 - 2.01	0.05

OR—odd ratio, CI—confidence interval.

6. Discussion

The prevalence of hyperuricemia for all participants in our study was 56.3%, and was higher in CKD than in HWCKD (75.4% vs 46.8%), as it was higher in males than females (63.7% vs 42.5%). The prevalence of hyperuricemia in HWCKD mirrors that found by Cannon *et al.* [27] but higher than the 41.4% (35% in males, 43% in females) found in a nationwide survey of Taiwanese hypertensives [28], higher than the 38.7% found in the Chinese hypertensive population [29], and much higher than the 14% reported by Fan *et al.* [30]. It is however lower than the 59.3% and 62% reported by Emokpae *et al.* [31] among males and female respectively, in a Nigerian hypertensive population.

Apart from variations in the diagnostic cut-off across population segments, differences in the methodology could be contributory. Our prevalence of hyperuricemia in CKD is similar to that that reported in a United State pediatric hypertensive population with 70%. It is higher than the 67% reported by Doualla *et al.* [5] in Cameroon, another low income nation, higher than the 47.5% found by Adejumon *et al.* [4] in Nigeria, higher than the 60% found in Italy, and much higher than the 15.2% reported in Chad. Our study population was made up of recently diagnosed hypertensives, and CKD patients who were not receiving uric acid lowering therapy (ULT). Our facility being a tertiary health care centre commonly receives cases in advance stages of disease. Our inclusion of non-dialytic stage 5 CKD patients also contributed to the high prevalence.

We found a higher prevalence of hyperuricemia in males than females and this is in agreement with findings by Alikor and Makususidi and their respective groups in Nigeria and Wang *et al.* in China [32] [33] [34]. Hyperuricemia is however reported to be more prevalent in females [28] [31] [35]. The higher prevalence in males in our study could be multifactorial. First, higher estrogen concentrations in females particularly premenopausal, confers on them higher uricosuric ability [32]. Though the use of alcohol and smoking was not assessed in this study, their use (and therefore higher risk for hyperuricemia) are reported to be commoner amongst males than females [32] [36]. The culture-enhancing socioeconomic advantage of men over women in our clime, makes them (men) more likely to take more meat (animal protein) than females [37]. The toxic ef-

fect of testosterone on the renal tubules further contributes to the greater decline in tubular uric acid secretion associated with increased sodium reabsorption in the proximal tubules [38].

The positive relationship between the age and the uric acid concentration (UAC) mirrors findings by Cameroon, and that by Avram *et al.* [5] [38] but is not in agreement with findings by Grayson *et al.* [35] and Lin *et al.* who reported higher UAC in the younger age groups. Even in health, the physiologic decline in kidney function from middle age is expected to lead to a relative kidney function decline with advancing age resulting in lower uric acid excretion. The relatively smaller volume of total body water (TBW) in the elderly would also contribute to a greater delivery of sodium to the distal tubules and an adaptive increase in sodium absorption coupled with decreased uric acid secretion in the PT [28].

We found a positive correlation between the BMI and UAC, and is in agreement with previous studies. Obesity induces hyperinsulinism associated with increased leptin production. Hyperinsulinemia cause increased absorption of sodium and urate in the proximal tubule leading to hypertension and hyperuricemia [39]. The synergistic effect of declining urate secretion from aging and increase absorption from hyperinsulinemia in our study could explain the higher uric acid in the elderly and in the overweight/obese, a combination that doesn't agree with finding from many previous studies [28] [29] [30].

The positive correlation between the uric acid levels and the blood pressure in our study agrees with previous studies that reported the link between hyperinsulinemia and hypertension. In animal models, hyperuricemia acutely induces increased renin production from the juxtaglomerular apparatus (JGA), suppresses both macula densa nitric oxide synthase (NOS) release and phosphorylation of endothelial nitric oxide (eNOS). The resultant release of reactive oxygen specie (ROS) and vasoconstrictive mediators, with increased sodium reabsorption at the PT lead to hypertension [40]. Continued chronic inflammatory damages from hyperuricemia lead to microvascular injury involving the afferent arterioles, increased smooth muscle reuptake of uric acid, activation of more chronic inflammatory mediators like monocyte chemo attractant protein-1 (MCP-1) and expression of cyclo-oxygenase-2 (COX-2) pathway [41]. These inflammatory processes create a chronic vasoconstrictive vascular bed with ischemia, hypertension, vascular stiffness and eventually, atherosclerosis as reported in the Generation 3 Framinghan study [42]. A cohort study of 3584 Japanese with prehypertension showed that hyperuricemia increased the risk of hypertension [43], Uric acid > 0.410 mmol/L predicted refractory hypertension in women older than 65 years (OR—3.11, 95% CI—1.06 - 9.0), independent of CKD [44] Imazu *et al.* in a systematic review, reported hyperuricemia in 25% - 40% of untreated hypertensives and in 70% of patients with malignant hypertension [45]. We found a positive relationship between proteinuria and the urate levels and this agrees with earlier studies [5] [46]. Proteinuria results, among other conditions,

from chronic immunologic injury to the glomerular filtration apparatus involving shedding of the endothelial surfaces into sub-epithelial spaces and replacement of the foot processes by continuous bands along the basement membrane. Although we didn't assess albumin loss in this study, it is worth noting that the resultant alteration in barrier selectivity and eventual cupping (fusion) of the cytoplasmic strands of the podocytes (effacement) leads to albuminuria/proteinuria [47]. The higher proteinuria in CKD compared to hypertension would therefore suggest a more intense immunologic response.

We found a positive correlation between hyperuricemia and anemia, as previously reported [48]. Anemia and hyperuricemia could be adjudged to be due to declining kidney function. Our study didn't seek to establish a link between these two, but McAdams DeMarco *et al.* [48] had reported that hyperuricemia cause anemia from oxidative stress, a feature common in the two conditions, and in CKD. Although the role of the hepatocytes in protein synthesis was not accessed in this study, the positive relationship between hyperuricemia and blood pressure on one hand, and its negative relationship with serum albumin on the other hand tend to favor proteinuria as the major cause of the hypoalbuminemia than reduced hepatic synthesis, in these cohorts. Due to the higher urea and creatinine among the CKD cohort compared with the hypertensives, coupled with the positive correlation between hyperuricemia and serum creatinine, we infer that proteinuria is a more likely cause of hypoalbuminemia than reduced hepatic synthesis in this cohort [49].

The higher degree of proteinuria and dyslipidemia in males in this study agrees with authors that reported that hypoproteinemia activates hepatic lipid synthesis leading to the release of, at times, excessive lipoprotein moieties in the blood (in a bit to maintain normal serum protein) including the more artherogenic forms of LDL [50]. Considering the role of the LDL subunits in atherosclerosis and its relationship with the blood pressure, the higher blood pressure found among the CKD cohorts in this study explain an initiating role for proteinuria in atherosclerosis and hypertension.

It is known that hyperuricemia results from over production and/or decline in excretion of urate. Overall, the positive relationship between hyperuricemia and, aging, elevated creatinine, elevated blood pressure and anemia (correlates of declining kidney function) is more is more suggestive of hyperuricemia arising from reduced excretion than from increased production [51].

This study was not without limitations. We couldn't assess proteinuria through the more sensitive spot Albustix Test. The relatively small sample size would limit the wider applicability of findings. Participants were not followed up to determine a cause and effect relationship between hyperuricemia and target organs or measures. As participants were recently diagnosed and not receiving ULT, the relationship between hyperuricemia and medications was not determined. The strength is in its assemblage of a wide range of variables that could be related, independently or in association to hyperuricemia in hypertension and CKD.

7. Conclusion

Hyperuricemia is very common in hypertension, more so, in CKD, commoner in males, advancing age and higher BMI. Correlates of hyperuricemia such as higher blood pressure, proteinuria and hypoalbuminemia, anemia and reduced kidney function were more prevalent in CKD than hypertension. Our findings suggested reduced urate excretion as the more likely cause of hyperuricemia than excessive intake. Studies aimed at finding causal relationships are needed to ascertain definitive interactions.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Mallat, S.G., Kattar, S.A., Tanios, B.Y. and Jurius, A. (2016) Hyperuricemia, Hypertension, and Chronic Kidney Disease: An Emerging Association. *Current Hypertension Reports*, **18**, 74. https://doi.org/10.1007/s11906-016-0684-z

[2] Stanifer, J.W., Jing, B., Tolan, S., Helmke, N., Mukerjee, R., Naicker, S., *et al.* (2014) The Epidemiology of Chronic Kidney Disease in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. *The Lancet Global Health*, **2**, e174-e181. https://doi.org/10.1016/S2214-109X(14)70002-6

[3] Mahamat, A.G., Hamat, I., Tondi, Z., Lemrabott, A., Faye, M., Moustapha, C., Sabi, K., Ka, K., Abdou, N. and Boucar, D. (2017) Hyperuricemia in Patients with Chronic Renal Failure in the General Hospital of National Reference of N'Djamena (Chad). *Open Journal of Nephrology*, **7**, 9-18. https://doi.org/10.4236/ojneph.2017.71002

[4] Adejumo, O., Okaka, E., Okwuonu, C. and Ojogwu, L. (2016) Hyperuricemia in Predialysis Chronic Kidney Disease Patients in Southern Nigeria. *Sahel Medical Journal*, **19**, 21-26. https://doi.org/10.4103/1118-8561.181890

[5] Doualla, M., Halle, M.P., Moutchia, J., Tegang, S. and Ashuntantang, G. (2018) Determinants of Hyperuricemia in Non-Dialysed Chronic Kidney Disease Patients in Three Hospitals in Cameroon. *BMC Nephrology*, **19**, 169. https://doi.org/10.1186/s12882-018-0959-5

[6] Mutluay, R., Deger, S.M., Bahadir, E., *et al.* (2012) Uric Acid Is an Important Predictor for Hypertensive Early Atherosclerosis. *Advances in Therapy*, **29**, 276-286. https://doi.org/10.1007/s12325-012-0006-z

[7] Lottmann, K., Chen, X. and Schädlich, P.K. (2012) Association between Gout and All-Cause as Well as Cardiovascular Mortality: A Systematic Review. *Current Rheumatology Reports*, **14**, 195-203. https://doi.org/10.1007/s11926-011-0234-2

[8] Kang, D.H. and Ha, S.K. (2014) Uric Acid Puzzle: Dual Role as Anti-Oxidant and

Pro-Oxidant. *Electrolytes & Blood Pressure*, **12**, 1-6. https://doi.org/10.5049/EBP.2014.12.1.1

[9] Spitsin, S. and Koprowski, H. (2010) Role of Uric Acid in Alzheimer's Disease. *Journal of Alzheimer's Disease*, **19**, 1337-1338. https://doi.org/10.3233/JAD-2010-1336

[10] Weisskopf, M.G., O'Reilly, E., Chen, H., Schwarzschild, M.A. and Ascherio, A. (2007) Plasma Urate and Risk of Parkinson's Disease. *American Journal of Epidemiology*, **166**, 561-567. https://doi.org/10.1093/aje/kwm127

[11] Rentzos, M., Nikolaou, C., Anagnostouli, M., *et al.* (2006) Serum Uric Acid and Multiple Sclerosis. *Clinical Neurology and Neurosurgery*, **108**, 527-531. https://doi.org/10.1016/j.clineuro.2005.08.004

[12] Nieto, F.J., Iribarren, C., Gross, M.D., Comstock, G.W. and Cutler, R.G. (2000) Uric Acid and Serum Antioxidant Capacity: A Reaction to Atherosclerosis? *Atherosclerosis*, **148**, 131-139. https://doi.org/10.1016/S0021-9150(99)00214-2

[13] Chalmers, J., MacMahon, S., Mancia, G., Whitworth, J., Beilin, L., Hansson, L., *et al.* (1999) 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Sub-Committee of the World Health Organization. *Clinical and Experimental Hypertension*, **21**, 1009-1060. https://doi.org/10.3109/10641969909061028

[14] Benn, C.L., Dua, P., Gurrell, R., Loudon, P., Pike, A., Storer, R.I., *et al.* (2018) Physiology of Hyperuricemia and Urate-Lowering Treatments. *Frontiers in Medicine*, **5**, 160. https://doi.org/10.3389/fmed.2018.00160

[15] Liyanage, T., Ninomiya, T., Jha, V., Neal, B., Patrice, H.M. and Okpechi, I. (2015) Worldwide Access to Treatment for End-Stage Kidney Disease: A Systematic Review. *The Lancet*, **385**, 1975-1982. https://doi.org/10.1016/S0140-6736(14)61601-9

[16] Feig, D.I., Soletsky, B. and Johnson, R.J. (2008) Effect of Allopurinol on Blood Pressure of Adoles-Cents with Newly Diagnosed Essential Hypertension: A Randomized Trial. *JAMA*, **300**, 924-932. https://doi.org/10.1001/jama.300.8.924

[17] Lee, J.W. and Lee, K.H. (2019) Comparison of Renoprotective Effects of Febuxostat and Allopurinol in Hyperuricemic Patients with Chronic Kidney Disease. *International Urology and Nephrology*, **51**, 467-473. https://doi.org/10.1007/s11255-018-2051-2

[18] National Kidney Foundation (2012) KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *American Journal of Kidney Diseases*, **60**, 850-886. https://doi.org/10.1053/j.ajkd.2012.07.005

[19] Emamian, S.A., Nielsen, M.B., Pedersen, J.F., *et al.* (1993) Kidney Dimensions at Sonography: Correlation with Age, Sex, and Habitus in 665 Adult Volunteers. *AJR. American Journal of Roentgenology*, **160**, 83-86. https://doi.org/10.2214/ajr.160.1.8416654

[20] Tsai, C.-W., Lin, S.-Y., Kuo, C.-C. and Huang, C.-C. (2017) Serum Uric Acid and Progression of Kidney Disease: A Longitudinal Analysis and Mini-Review. *PLoS ONE*, **12**, e0170393. https://doi.org/10.1371/journal.pone.0170393

[21] Meng, L., Yu, W., Wang, T., Zhang, L., Heerdt, P. and Gelb, A.W. (2018) Blood Pressure Targets in Perioperative Care. Provisional Considerations Based on a Comprehensive Literature Review. *BMJ Hypertension*, **72**, 806-817. https://doi.org/10.1161/HYPERTENSIONAHA.118.11688

[22] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) Third Report of the National Cholesterol Education Program (NCEP)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*, **106**, 3143-3421. https://doi.org/10.1161/circ.106.25.3143

[23] Cappellini, M.D. and Mota, I. (2015) Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change with Aging? *Seminars in Hematology*, **52**, 261-269. https://doi.org/10.1053/j.seminhematol.2015.07.006

[24] Boag, A.M., Breheny, C., Handel, I. and Gow, A.G. (2019) Evaluation of the Effect of Urine Dip vs Urine Drip on Multi-Test Strip Results. *Veterinary Clinical Pathology*, **48**, 276-281. https://doi.org/10.1111/vcp.12730

[25] Kim, S., McClave, S.A., Martindale, R.G., Miller, K.R. and Hurt, R.T. (2017) Hypoalbuminemia and Clinical Outcomes: What Is the Mechanism behind the Relationship? *The American Surgeon*, **83**, 1220-1227. https://doi.org/10.1177/000313481708301123

[26] Levey, A.S., Stevens, L.A., Schmid, C.H., Zhang, Y.L., Feldman, H.I., Eggers, P., Van Lente, F., Greene, T., *et al.* (2009) A New Equation to Estimate Glomerular Filtration Rate. *Annals of Internal Medicine*, **150**, 604-612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

[27] Cannon, P.J., Stason, W.B., Demartini, F.E., Sommers, S.C. and Laragh, J.H. (1966) Hyperuricemia in Primary and Renal Hypertension. *NEJM*, **275**, 457-464. https://doi.org/10.1056/NEJM196609012750902

[28] Lin, C.S., Lee, W.L., Hung, Y.J., Lee, D.Y., Chen, K.F., Chi, W.C., *et al.* (2012) Prevalence of Hyperuricemia and Its Association with Antihypertensive Treatment in Hypertensive Patients in Taiwan. *International Journal of Cardiology*, **56**, 41-46. https://doi.org/10.1016/j.ijcard.2010.10.033

[29] Liu, J., Chen, L., Yuan, H., Huang, K., Li, G., Sun, N., *et al.* (2021) Survey on Uric Acid in Chinese Subjects with Essential Hypertension (SUCCESS): A Nationwide Cross-Sectional Study. *Annals of Translational Medicine*, **9**, 27. https://doi.org/10.21037/atm-20-3458

[30] Fan, X.H., Sun, K., Wang, Y.B., Dang, A.M., Zhou, X.L., Zhang, H.M., *et al.* (2009) Prevalence and Associated Risk Factors of Hyperuricemia in Rural Hypertensive Patients. *Chinese Medical Journal*, **89**, 2667-2670.

[31] Emokpae, A. and Abdul, A. (2013) Serum Uric Acid Levels among Nigerians with Essential Hypertension. *Nigerian Journal of Physiological Sciences*, **28**, 41-44.

[32] Alikor, C.A. and Emem-Chioma, P.C. (2013) Prevalence of Hyperuricaemia in a Rural Population in Nigeria Niger Delta Region. *Nigerian Journal of Medicine*, **22**, 187-192.

[33] Makusidi, M.A., Chijioke, A., Kolo, P.M., Liman, H.M., AbdulRahman, M.B., Sani, B., *et al.* (2016) Prevalence and Pattern of Hyperuricemia in a Survey among Inhabitants of Sokoto Metropolis, North Western Nigeria. *Research Journal of Health Sciences*, **4**, 1.

[34] Wang, S.F., Shu, L., Wang, S., Wang, X.Q., Mu, M. and Hu, C.Q. (2014) Gender Difference in the Association of Hyperuricemia with Hypertension in a Middle-Aged Chinese Population. *Blood Pressure*, **23**, 339-344. https://doi.org/10.3109/08037051.2014.906131

[35] Grayson, P.C., Kim, S.Y., LaValley, M. and Choi, H.K. (2011) Hyperuricemia and Incident Hypertension: A Systematic Review and Meta-Analysis. *Arthritis Care & Research*, **63**, 102-110. https://doi.org/10.1002/acr.20344

[36] Ewenighi, C.O., Dimkpa, U., Ezeugwu, U., Onyeanusi, J., Onoh, L. and Adejumo, B. (2015) Prevalence of Hyperuricemia and Its Risk Factors in Healthy Male Adults

from Abakaliki Metropolis, Nigeria. *Journal of Molecular Pathophysiology*, **4**, 94-98. https://doi.org/10.5455/jmp.20150915011842

[37] Ulasi, I. (2008) Gender Bias in Access to Healthcare in Nigeria: A Study of End Stage Renal Disease. *Tropical Doctor*, **38**, 50-52. https://doi.org/10.1258/td.2007.060160

[38] Verzola, D., Gandolfo, M.T., Salvatore, F., Villaggio, B., Gianiorio, F., Traverso, P., *et al.* (2004) Testosterone Promotes Apoptotic Damage in Human Renal Tubular Cells. *Kidney International*, **65**, 1252-1261. https://doi.org/10.1111/j.1523-1755.2004.00497.x

[39] Avram, Z. and Krishnan, E. (2008) Hyperuricaemia—Where Nephrology Meets Rheumatology. *Rheumatology* (*Oxford*), **47**, 960-964. https://doi.org/10.1093/rheumatology/ken070

[40] Stewart, D.J., Langlois, V. and Noone, D. (2019) Hyperuricemia and Hypertension: Links and Risks. *Integrated Blood Pressure Control*, **12**, 43-62. https://doi.org/10.2147/IBPC.S184685

[41] Goicoechea, M., Garcia de Vinuesa, S., Verdalles, U., Verde, E., Macias, N., Santos, A., *et al.* (2015) Allopurinol and Progression of CKD and Cardiovascular Events: Long-Term Follow-up of a Randomized Clinical Trial. *American Journal of Kidney Diseases*: *The Official Journal of the National Kidney Foundation*, **65**, 543-549. https://doi.org/10.1053/j.ajkd.2014.11.016

[42] Mehta, T., Nuccio, E., McFann, K., Madero, M., Sarnak, M.J. and Jalal, D. (2015) Association of Uric Acid with Vascular Stiffness in the Framingham Heart Study. *American Journal of Hypertension*, **28**, 877-883. https://doi.org/10.1093/ajh/hpu253

[43] Kuwabara, M., Hisatome, I., Niwa, K., Hara, S., Roncal-Jimenez, C.A., Bjomstad, P., *et al.* (2018) Uric Acid Is a Strong Risk Marker for Developing Hypertension from Prehypertension: A 5-Year Japanese Cohort Study. *Hypertension*, **71**, 78-86. https://doi.org/10.1161/HYPERTENSIONAHA.117.10370

[44] Mazza, A., Lenti, S., Schiavon, L., Monte, A.D., Townsend, D.M., Ramazzina, E., *et al.* (2017) Asymptomatic Hyperuricemia Is a Strong Risk Factor for Resistant Hypertension in Elderly Subjects from General Population. *Biomedicine & Pharmacotherapy*, **86**, 590-594. https://doi.org/10.1016/j.biopha.2016.11.104

[45] Imazu, M., Yamamoto, H., Toyofuku, M. and Sumii, K. (2002) Hyperinsulinemia for the Development of Hypertension: Data from the Hawaii-Los Angeles-Hiroshima Study. *Hypertension Research*, **24**, 531-536. https://doi.org/10.1291/hypres.24.531

[46] Biyik, Z. and Guney, I. (2018) Relationship between Uric Acid, Proteinuria, and Atherogenic Index of Plasma in Renal Transplant Patients. *Transplantation Proceedings*, **50**, 3376-3380. https://doi.org/10.1016/j.transproceed.2018.05.021

[47] Jayasinghe, K., White, S.M., Kerr, P.G., MacGregor, D., Stark, Z., Wilkins, E., *et al.* (2019) Isolated Proteinuria Due to CUBN Homozygous Mutation—Challenging the Investigative Paradigm. *BMC Nephrology*, **20**, 330. https://doi.org/10.1186/s12882-019-1474-z

[48] McAdams-DeMarco, M.A., Maynard, J.W., Coresh, J. and Baer, A.N. (2012) Anemia and the Onset of Gout in a Population-Based Cohort of Adults: Atherosclerosis Risk in Communities Study. *Arthritis Research & Therapy*, **14**, R193. https://doi.org/10.1186/ar4026

[49] Kuwabara, M., Niwa, K., Nishi, Y., Mizuno, A., Asano, T., Masuda, K., *et al.* (2014) Relationship between Serum Uric Acid Levels and Hypertension among Japanese Individuals Not Treated for Hyperuricemia and Hypertension. *Hypertension Re-*

search, **37**, 785-789. https://doi.org/10.1038/hr.2014.75

[50] Kuwabara, M., Niwa, K., Nishi, Y., Hisatome, I., *et al.* (2011) The Positive Relationship between Uric Acid and Hypertension in Japanese People Not Taking Antihypertensive Drugs. *Journal of Hypertension*, **29**, e32-e33. https://doi.org/10.1097/01.hjh.0000408079.36559.0f

[51] Bulbul, M.C., Dagel, T., Afsar, B., Ulusu, N.N., Kuwabara, M., Covid, A., *et al.* (2018) Disorders of Lipid Metabolism in Chronic Kidney Disease. In-Depth Review. *Blood Purification*, **46**, 144-152. https://doi.org/10.1159/000488816

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