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Foreword

Foreword by Editor-in-Chief

Prof. Nataliya Bhinder

Greetings to all readers of the Annals of Innovation in Medicine,

As we commence the first issue of the Annals for the year 2024, it is my privilege to introduce this latest compilation of groundbreaking research and transformative ideas in the field of medicine.

In a world where medical science is advancing at an unprecedented pace, the need for innovation in healthcare has never been more pressing. The Annals of Innovation in Medicine serves as a platform for disseminating cutting-edge discoveries, pioneering technologies, and visionary approaches that are shaping the future of healthcare delivery and patient outcomes.

Within these pages, you will find a diverse array of articles spanning a wide range of medical disciplines, each offering unique perspectives and insights into the challenges and opportunities facing modern medicine. From groundbreaking research studies to innovative clinical interventions, the articles in this volume represent the collective efforts of researchers, clinicians, and healthcare professionals dedicated to advancing the frontiers of medical knowledge and practice.

As editors, we extend our heartfelt appreciation to the authors for their invaluable contributions and to the reviewers for their diligent evaluation, which have ensured the quality and relevance of the published work.

To our esteemed readers, we invite you to explore the pages of the Annals with curiosity and an open mind. May the discoveries and insights contained herein inspire new ideas, foster collaboration, and ultimately lead to improved patient care and outcomes.

With warm regards,

Nataliya Bhinder

Editor-in-Chief

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Research Article

Effects of Administration of Bouillon Cubes on Insulin Resistance, Lipid Profile and Renal Function Parameters in Female Albino Rats

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Abstract:

Aim: To evaluate the effects of administration of bouillon cubes on insulin resistance, lipid profile and renal function parameters in female albino rats.

Methodology: A total of thirty-five (35) female albino rats, weighing between 120 and 150 grams, were used for the study. The bouillon cubes, Star Maggi and Knorr were administered daily to the rats, using an oral gavage tube for 90days. Fasting plasma glucose (FPG) was determined using the Glucose oxidase method. Fasting plasma insulin (FPI) and Cystatin C levels were quantitatively determined by a rat-specific sandwich-enzyme linked immunosorbent assay (ELISA) method. Insulin resistance was determined using the homeostatic model assessment for insulin resistance (HOMA-IR) method. The electrolytes, sodium (Na+) and potassium (K+) and were determined using ion selective electrode method. Urea was determined using Urease-bertholet method. Creatinine was determined using the Jaffe-Slot method. Total Cholesterol (TC), Triglyceride (TG) and High-Density Lipoprotein Cholesterol (HDL-C) were determined by enzymatic methods. Low Density Lipoprotein Cholesterol (LDL-C) was calculated from the Friedewald's equation. Kidney sections were stained using haematoxylin and eosin (H&E) staining technique. Quantitative analysis of monosodium glutamate (MSG) content of the bouillon cubes was analyzed using ultraviolet (UV) spectroscopy while the sodium content was analyzed using atomic absorption spectrophotometry according to the method of the American Public Health Association.

Results: There were no significant differences (P>.05) in FPG, FPI and HOMA-IR in all the treatment groups. The mean cystatin C value in group E (High Dose Knorr) was significantly higher (P <.05) than the negative control and all other treatment groups. The results also show the mean sodium values in groups D (High Dose Maggi) and E (High Dose Knorr) were significantly lower (P <.05) when compared to the negative control. There were no significant differences (P >.05) in TC and HDL-C levels in the negative control, compared to the treatment groups. There were no significant differences (P >.05) in TG levels, except for group B (Low Dose Maggi) which significantly lower (P <.05) than the negative control. Also, there were no significant differences (P >.05) in LDL-C levels, except for group B (Low Dose Maggi) which significantly higher (P <.05) than the negative control. Histologic analysis of the kidneys of the treated groups showed histological changes in the architecture of the tissues indicating tissue distortion, acute tissue damage, glomerular nephritis and distorted capillaries and degeneration compared to the negative control group which showed no tissue distortion.

Conclusion: Chronic exposure to bouillon cubes did not impact fasting plasma glucose, insulin and insulin resistance in the treated rats. Chronic administration of Knorr cubes impacted the integrity of the kidney as levels of cystatin C and sodium were altered in the albino rats. Histoarchitecture of the kidneys of the treated rats showed histological changes indicating tissue distortion, acute tissue damage, glomerular nephritis and distorted capillaries. Lipid profile/metabolism was relatively not affected by the administration of bouillon cubes.

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Keywords: Monosodium glutamate; Bouillon cubes; Renal function; Lipid profile; Insulin resistance.

1. INTRODUCTION

Bouillon cubes serve as flavour enhancers, elevating the taste and aroma of food and adding a touch of culinary artistry to the preparation of delicious dishes. Across various African countries, these cubes have become essential components in everyday cooking. Nestlé Company reports that over 100 million bouillon cubes are purchased daily in the West Central Africa region, underscoring their widespread use and popularity [1,2].

Numerous brands of bouillon cubes populate the market, including Star Maggi, Knorr Cubes, Royco, Onga, Aji-no-Moto, and others. Maggi and Knorr bouillon cubes, which are the most common brands, typically consist of a dehydrated broth or mixture condensed into cube form, and these same blends can also be found in powdered form. Despite their lower nutritional content, these cubes have largely replaced many fermented seeds and products, which once contributed diverse flavours and nutritional value to African dishes. Experts liken bouillon cubes to "well-packaged salts," and studies suggest that prolonged exposure to these cubes may have adverse health effects due to their primary ingredients. One of the contents of bouillon cubes which has attracted interest and is of concern is monosodium glutamate (MSG), which has been implicated in toxicity to different organ systems [3, 4].

As health consciousness rises, there is an increased demand for products promoting better well-being. Consequently, bouillon cubes being integral to the food consumed, have come under scrutiny, particularly in our country, Nigeria [5]. This study evaluates the effects of administration of bouillon cubes on insulin resistance, lipid profile and renal function parameters in female albino rats. This research may contribute in understanding the health impact of bouillon cubes, and promote responsible consumption and production by informing decisions related to food safety and regulation, in line with the Sustainable Development Goals (SDGs).

2. MATERIALS AND METHODS

2.1 Experimental Animals

A total of thirty-five (35) female albino rats, weighing between 120 and 150 grams, was used for the study. The rats were kept in standard cages and provided with unrestricted access to feed and water. A period of 14 days was allotted for the animals to acclimatize before the study officially began.

2.2 Treatments

Two (2) commonly used bouillon cubes (Star Maggi and Knorr cubes) purchased from the local market in Port Harcourt were used for the study. They are readily available brands, with a high patronage. Maggi cube is manufactured by Nestle Nigeria PLC, Industrial Avenue 22/24 Ilupeju, Lagos Nigeria. Knorr cube is manufactured by Unilever PLC, RC 113 Agbara Industrial Estate, Agbara, Ogun State, Nigeria

2.3 Acute Toxicity Study

This was done using the fixed dose procedure [6]. Eighteen (18) rats were divided into six (6) groups of three (3) rats each – 3 groups for Maggi and 3 groups for Knorr. 2000mg/kg, 3000mg/kg, and 5000mg/kg of star Maggi cube was administered to the rats in groups 1, 2, and 3 respectively while 2000mg/kg, 3000mg/kg, and 5000 mg/kg of Knorr cube was administered to the rats in groups 4, 5, and 6 respectively. The rats were observed for signs of toxicity for 48 hours. After observation for 48 hours, there were no signs of toxicity, hence the bouillon cubes were considered safe up to a dose of 5000 mg/kg. For the study, 1500 mg/kg and 3000 mg/kg were adopted and used as low and high doses respectively.

2.4 Dose Calculation

2.4.1 Low Dose Maggi (1500 mg/kg)

1500mg/kg of Maggi was administered to the rats daily. That is, a 1kg would take 1500mg of Maggi. Therefore, a 150g rat took 150g /1000g x 1500mg = 225mg of Maggi as daily dose. A 1kg rat would take as vehicle 10 ml of fluid orally. Therefore, a 150g rat took 150g / 1000g x 10 ml = 1.5ml. Hence, 225mg of Maggi was dissolved in 1.5ml of water and administered daily. That is, 150 mg/ml. A stock solution was therefore prepared and administered according to the weight of the rats daily [6, 7].

2.4.2 High Dose Maggi (3000 mg/kg)

3000 mg/kg of Maggi was administered to the rats daily. That is, a 1kg would take 3000mg of Maggi. Therefore, a 150g rat took 150g /1000g x 3000mg = 450mg of Maggi as daily dose. A 1kg rat would take as vehicle 10 ml of fluid orally. Therefore, a 150g rat took 150g / 1000g x 10 ml = 1.5ml. Hence, 450mg of Maggi was dissolved in 1.5ml of water and administered daily. That is, 300mg/ml. A stock solution was therefore prepared and administered according to the weight of the rats daily [6, 7].

2.4.3 Low Dose Knorr (1500 mg/kg)

1500mg/kg of Knorr was administered to the rats daily. That is, a 1kg would take 1500mg of Knorr. Therefore, a 150g rat took 150g /1000g x 1500mg = 225mg of Knorr as daily dose. A 1kg rat would take as vehicle 10 ml of fluid orally. Therefore, a 150g rat took 150g / 1000g x 10 ml = 1.5ml. Hence, 225mg of Knorr was dissolved in 1.5ml of water and administered daily. That is, 150 mg/ml. A stock solution was therefore prepared and administered according to the weight of the rats daily [6, 7].

2.4.4 High Dose Knorr (3000 mg/kg)

3000mg/kg of Knorr was administered to the rats daily. That is, a 1kg would take 3000mg of Knorr. Therefore, a 150g rat took 150g /1000g x 3000mg = 450mg of Knorr as daily dose. A 1kg rat would take as vehicle 10 ml of fluid orally. Therefore, a 150g rat took 150g / 1000g x 10 ml = 1.5ml. Hence, 450mg of Knorr was dissolved in 1.5ml of water and administered daily. That is, 300mg/ml. A stock solution was therefore prepared and administered according to the weight of the rats daily [6, 7].

2.5 Experimental Design

The rats were weighed and divided into five (5) experimental groups (7 rats each) consisting of the negative control group (Group A) and 4 treatment groups (Groups B-E). The bouillon cubes were prepared into suspension form of 150mg/ml of bouillon cubes (Star Maggi and Knorr cubes) respectively for Low Doses and 300mg/ml of bouillon cubes (Star Maggi and Knorr cubes) for High Doses. The suspension was given daily using an oral gavage tube for 90days. Treatments were performed according to the grouping below;

Group A (Negative control group): Received no treatment.

Group B (Low dose Maggi): Received daily oral dose of 1500mg/kg Star Maggi cubes.

Group C (Low dose Knorr): Received daily oral dose of 1500 mg/kg Knorr cubes.

Group D (High dose Maggi): Received daily oral dose of 3000 mg/kg Star Maggi cubes.

Group E (High dose Knorr): Received daily oral dose of 3000 mg/kg Knorr cubes.

On the 91st day, the animals were fasted for 6 hours anaesthetized and later sacrificed. Blood was collected from each rat by means of cardiac puncture. All the animal experiments were conducted according to the ethical norms approved by the Institutional Ethical Committee.

2.6 Reagents and Biochemical Analyses

All reagents were purchased commercially and the standard operating procedures provided by the manufacturers were meticulously adhered to. Quality control (QC) samples were analyzed alongside the biochemical tests. Fasting plasma glucose (FPG) was determined using the Glucose oxidase method [8] as described by Spectrum Diagnostics (Egypt). Fasting plasma insulin (FPI) and Cystatin C levels were quantitatively determined by a rat-specific sandwich-enzyme linked immunosorbent assay (ELISA) method [9] as described by as described by Calbiotech Company limited, China. Insulin resistance (IR) was determined using the homeostatic model assessment for insulin resistance (HOMA-IR) method [10]. The electrolytes, sodium ($Na+$) and potassium (K^+) and were determined using ion selective electrode (ISE) method [11]. Urea was determined using Urease-bertholet method [12], as modified by Spectrum Diagnostics (Egypt). Creatinine was determined using the Jaffe-Slot method [13], as modified by Spectrum Diagnostics (Egypt). Total Cholesterol (TC) was determined by enzymatic method [14], as modified by Spectrum Diagnostics (Egypt). Triglyceride was determined by enzymatic method [15], as described by Spectrum Diagnostics (Egypt). High Density Lipoprotein Cholesterol (HDL-C) was determined by enzymatic method [16], as modified by Spectrum Diagnostics (Egypt). Low Density Lipoprotein Cholesterol (LDL-C) was calculated from the Friedewald's equation [17]. Quantitative analysis of monosodium glutamate (MSG) content of the bouillon cubes was analyzed using ultraviolet (UV) spectroscopy while the sodium content was analyzed using atomic absorption spectrophotometry according to the method of the American Public Health Association (APHA) [18]. Kidney specimens were harvested and fixed in 10% formal saline for histological analysis using Haematoxylin and Eosin stain, viewed and photomicrographs of the kidney were captured with X40 objective lens using the ScopeTekTM device and software v1.3.

2.7. Statistical Analysis

The data generated was analyzed with GraphPad Prism version 8.0.2. Analysis of variance (ANOVA) and Tukey's post hoc test were performed to compare differences between groups. The results were considered statistically significant at the 95% confidence interval ($p \leq 0.05$). Results are expressed as mean ± SD.

3. RESULTS AND DISCUSSION

Table 1: Quantitative Analysis of MSG and Sodium Content in the Bouillon Cubes

Samples	MSG Conc. (mg/g)	Sodium Conc. (ppm)
Star Maggi	119.636 (11.96%)	38.282 (0.00383 %)
Knorr Cube	111.455 (11.15%)	32.892 (0.00329 %)

Table 1 shows the results of Monosodium Glutamate (MSG) and sodium content of bouillon cubes. It shows that star Maggi had the highest contents of Monosodium Glutamate (MSG) with a concentration of 119.96 mg/g (11.96 %) while that of Beef Knorr cubes is 111.5 mg/g (11.15 %). The results also reveal that star Maggi had the highest sodium content with a concentration of 38 ppm (0.00383 %) while Knorr cube sodium content concentration is 32 ppm (0.00329 %).

These values were compared to the maximum allowable limits set by the National Agency for Food and Drug Administration and Control (NAFDAC), which are 1.5% max for MSG and 12.5% max for sodium in bouillon cubes. From the results above, the sodium content in both the Star Maggi and Beef Knorr cubes falls well within the permissible limit of 12.5%. However, the MSG content in both products exceeds the maximum allowable limit of 1.5% specified by NAFDAC, indicating consumers maybe at risk of toxicity from MSG. Even though the sodium content in the Star Maggi and Beef Knorr cubes is within the NAFDAC limit, it is still crucial to consider the cumulative sodium intake from other food items to stay within the recommended daily limits of less than 2g per day [19]. This is in consonance with the works of Apkanyung [20], and Alonge *et al.* [21], in which they found variable amounts of MSG, sodium, iron and zinc in bouillon cubes produced in Nigeria.

Table 2: Levels of the Fasting Plasma Glucose, Insulin and Insulin Resistance of the Rats after Treatment

Groups (N=7)	FPG (mmol/L)	FPI (mU/L)	HOMA-IR
Group A (Neg. Cont)	5.00 ± 0.85	1.90 ± 0.16	0.42 ± 0.04
Group B (Low Dose Maggi)	5.03 ± 0.65	2.47 ± 0.25	0.55 ± 0.07
Group C (Low Dose Knorr)	4.27 ± 0.38	2.53 ± 0.17	0.48 ± 0.06
Group D (High Dose Maggi)	4.15 ± 0.37	2.22 ± 0.30	0.41 ± 0.06
Group E (High Dose Knorr)	5.10 ± 0.42	2.12 ± 0.20	0.48 ± 0.05
P-value	0.0533	0.2992	0.3229
Summary	NS	NS	NS

N= number of rats, NS= not significant

From Table 2, the results from the study showed no significant differences ($P>.05$) in fasting plasma glucose (FPG), fasting plasma insulin (FPI), and HOMA-IR (Homeostatic model assessment of insulin resistance), in all the treatment groups of rats administered with varying inclusion of bouillon cubes when compared to the negative control group. These results showed that chronic exposure to bouillon cubes did not affect the glucose metabolism and insulin resistance of the rats. Therefore, indicating bouillon cubes (star Maggi and Knorr cubes) may not a predisposing factor to insulin resistance and type 2 diabetes. Insulin resistance is a key factor in the development of type 2 diabetes. It is presented as a suppression in metabolic responses of the liver, muscle, and adipose tissue to insulin action. It leads to impaired regulation of hepatic glucose synthesis, declining beta-cell function, ultimately leading to beta-cell failure [22]. This finding agrees with Tchaou et al. [23], which showed that overnight fasting glucose was not influenced by monosodium glutamate (MSG) and Maggi poulet solution injection. Another study found no effects of MSG administration on postprandial glycaemia and insulinemia [24], however, MSG-obese rats had impaired glucose tolerance and insulin resistance [25].

Table 3: Showing Levels of the Renal Function Markers of the Rats after Treatment

Groups (N=7)	Cystatin C (ng/mL)	Sodium (mmol/L)	Potassium (mmol/L)	Urea (mmol/L)	Creatinine (µmol/L)
Group A (Neg. Cont)	0.35 ± 0.06	146.00 ± 2.45	3.55 ± 0.40	4.82 ± 0.17	89.25 ± 1.26
Group B (Low Dose Maggi)	0.37 ± 0.08 ^{be}	138.3 ± 1.52	3.62 ± 0.20	4.43 ± 0.69	99.33 ± 1.96
Group C (Low Dose Knorr)	0.30 ± 0.06 ^{ce}	138.5 ± 3.41	4.77 ± 0.80	4.80 ± 0.42	116.8 ± 2.66
Group D (High Dose Maggi)	0.50 ± 0.10 ^{de}	128.8 ± 1.65 ^{ad}	3.02 ± 0.28	4.70 ± 0.53	104.8 ± 4.19
Group E (High Dose Knorr)	1.12 ± 0.13 ^{ae}	130.2 ± 2.33 ^{ae}	5.12 ± 0.85	4.72 ± 0.47	97.50 ± 3.07
P-value	0.0004	0.0006	0.1245	0.8424	0.0743
Summary	S	S	NS	NS	NS

N= number of rats, $^{ae, ad}$ =significant vs Neg. control, ^{be} = Group E significant Vs B, ^{ce} = Group E significant Vs C, ^{de} = Group E significant Vs D, NS= not significant.

From Table 3, the results showed the mean cystatin C value (1.12 ± 0.13 ng/mL) in group E (High Dose Knorr) was significantly higher ($P<.05$) than the negative control and all other treatment groups. The results also show the mean sodium values in groups D (High Dose Maggi) and E (High Dose Knorr) were significantly lower ($P<.05$) when compared to the negative control. There were no significant differences ($P>.05$) in Potassium, Urea and Creatinine in the treatment groups, compared to the negative control. The results indicate acute renal damage in the group administered High dose of Knorr cubes, due to the elevated cystatin C, a marker of acute kidney injury. Creatinine and urea are not significantly different, as they may take longer periods to indicate kidney injury. Studies suggest that chronic MSG intake induces kidney damage by oxidative stress with unclear underlying mechanisms. However, excessive renal metabolism of glutamate in chronic MSG intake can be a source of ROS,

which may damage renal tissue and cause renal impairment [26]. In a similar study. MSG had adverse effects on kidney functions as serum urea and serum creatinine were significantly increased. These effects were however, counteracted by the administration of vitamins C and E [27].

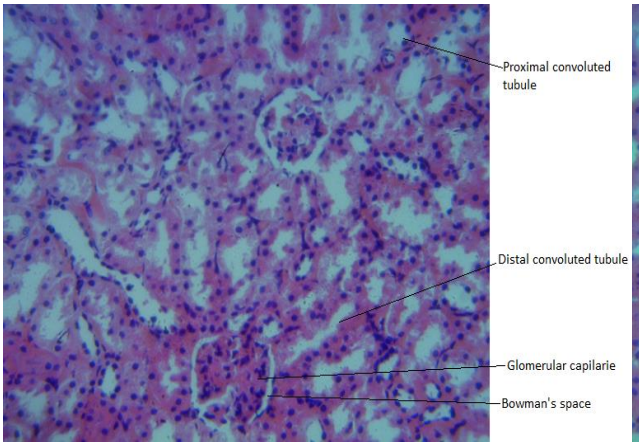
Table 4: Levels of the Lipid Profile Markers of the Rats after Treatments

Groups (N=7)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Group A (Neg. Cont)	2.55 ± 0.31	1.38 ± 0.30	1.62 ± 0.07	0.30 ± 0.05
Group B (Low Dose Maggi)	2.40 ± 0.15	0.72 ± 0.06 [ab]	1.50 ± 0.04	0.57 ± 0.04 [ab]
Group C (Low Dose Knorr)	2.20 ± 0.18	1.02 ± 0.04	1.40 ± 0.07	0.34 ± 0.06 [bc]
Group D (High Dose Maggi)	2.50 ± 0.18	1.06 ± 0.06	1.60 ± 0.07	0.42 ± 0.03
Group E (High Dose Knorr)	2.45 ± 0.30	1.22 ± 0.08 [be]	1.45 ± 0.13	0.44 ± 0.03
P-value	0.1484	0.0004	0.2047	0.0036
Summary	NS	S	NS	S

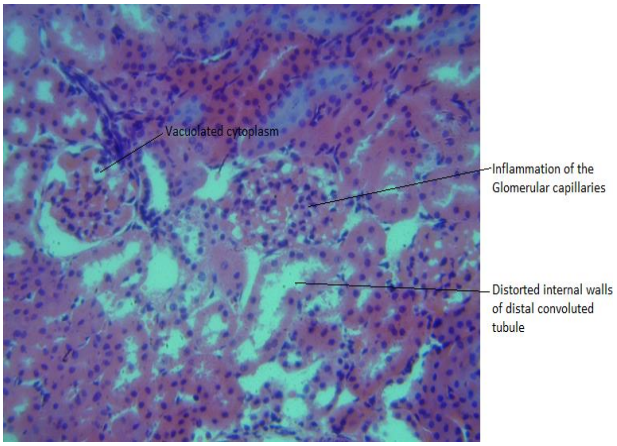
N= number of rats, [ab] =significant vs Neg. control, [be] = E significantly Vs B, [bc] = C significantly Vs B, NS= not significant

Table 4 shows results of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in the rats after treatment. The results show there were no significant differences ($P > .05$) in total cholesterol and HDL-C levels in the negative control, compared to the treatment groups. There were no significant differences ($P > .05$) in triglyceride levels, except for group B (Low Dose Maggi) which significantly lower ($P < .05$) than the negative control. Also, there were no significant differences ($P > .05$) in low density lipoprotein cholesterol levels, except for group B (Low Dose Maggi) which significantly higher ($P < .05$) than the negative control. The results indicate lipid metabolism was relatively not affected by the administration of bouillon cubes. In similar studies, MSG exposed albino rats had significantly increased serum triglycerides, total and LDL cholesterol levels [26,28.29]. in many of these studies however, MSG was administered directly, not as seasoning cubes.

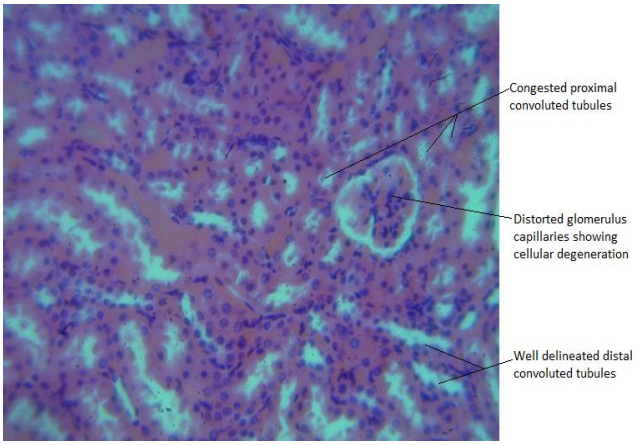
Histologic analysis of the kidney of the treated groups showed histological changes in the architecture of the tissues indicating tissue distortion, acute tissue damage, glomerular nephritis and distorted capillaries and degeneration compared to the negative control group which showed no tissue distortion. Group B (Low Dose Maggi) showed dilated glomerular capillaries indicating cellular hyperplasia and congested renal vessels. The tissues show hypertrophy of luminal epithelia of distal convoluted tubules. Group C (Low Dose Knorr) showed tissue damage. The glomeruli capillary cells show degeneration and cell death. Several vacuoles observed within the glomeruli. The High Dose Maggi group showed shrinkage of the glomerular capillaries with bowman's space. The glomerular cells appear pyknotic. Proximal and distal convoluted tubules appear normal. Glomerular nephritis is indicated. The High dose Knorr group showed distorted glomerular capillaries and cellular degeneration. The distal convoluted tubules show no distortion but mild congestions are observed in the proximal convoluted tubules. In our previous study, we reported changes in the architecture of the hepatocytes of the rats, indicating moderate dilation of the central vein, moderate disruption of the hepatic lobules, and mild sinusoidal dilation, after chronic administration of bouillon cubes [30]. In similar studies, Paul et al. [26] reported morphological changes in liver (central venous congestion, diffuse degeneration, necrosis of hepatocytes) and cortical tubular degeneration in the kidney of albino rats. In another study, MSG treated rats showed disorganized renal structure; shrunken glomerular tufts with dilatation of the capsular space, vacuolated cytoplasm of tubular cells with periglomerular fibrosis and interstitial nephritis. [31,32].



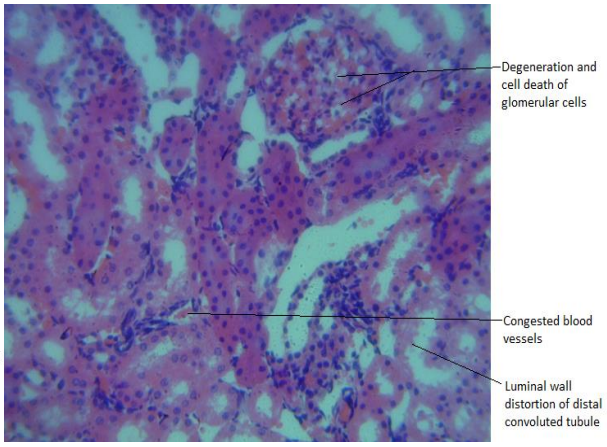
Group A (a)



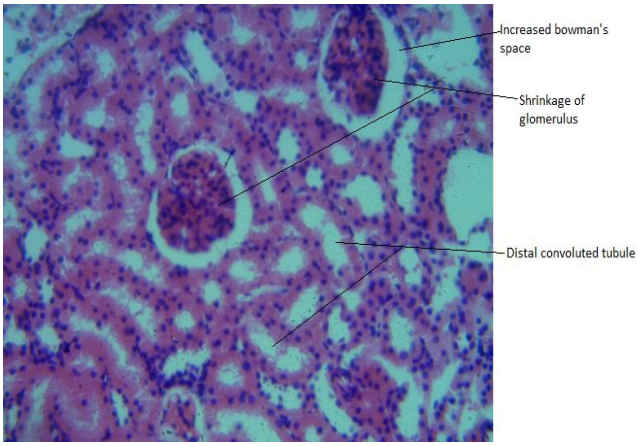
Group B (b)



Group C (c)



Group D (d)



Group E (e)

Figure 1(a), (b), (c), (d) and (e). Shows photomicrograph (X 400) of H&E-stained histologic sections of the Kidney of the rats. The negative control (a) shows normal histoarchitecture of the glomerular capillaries, Bowman's capsule and distal convoluted tubule. Kidney tissue showed no distortion. The Low Dose Maggi group (b) showed dilated glomerular capillaries indicating cellular hyperplasia and congested renal vessels. Tissues show hypertrophy of luminal epithelia of distal convoluted tubules. Tissue distortion (arrows). The Low Dose Knorr group (c) showed tissue damage. The glomeruli

capillaries cells show degeneration and cell death. Several vacuoles observed within the glomeruli. Acute tissue damage (arrows). The High Dose Maggi group (d) showed shrinkage of the glomerular capillaries with bowman's space. The glomerular cells appear pyknotic. Proximal and distal convoluted tubules appear normal. Glomerular nephritis is indicated. The High Dose Knorr group (e) showed distorted glomerular capillaries and cellular degeneration. The distal convoluted tubules show no distortion but mild congestions are observed in the proximal convoluted tubules.

4. CONCLUSION

Chronic exposure to bouillon cubes did not impact fasting plasma glucose, insulin and insulin resistance in the treated rats. Chronic administration of Knorr cubes impacted the integrity of the kidney as levels of cystatin C and sodium were altered in the albino rats. Histoarchitecture of the kidneys showed histological changes indicating tissue distortion, acute tissue damage, glomerular nephritis and distorted capillaries. Lipid profile/metabolism was relatively not affected by the administration of bouillon cubes. The usage of bouillon cubes should be moderated, considering their potential impact on long-term health and well-being. Local authorities need to verify the components of bouillon cubes to guarantee consumer safety.

Competing Interests

The authors have affirmed the absence of any competing interests.

Authors' Contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Limitations of the Study

This study was initially designed as a human study, however with issues surrounding the actual dose of the bouillon cubes consumed, and follow-up of human subjects in a resource limited setting, the animal study was adopted. Hence, human studies are encouraged to carried on the cubes. Although initial toxicity in animals is a better choice as it allows use of higher dosages, but follow-up human studies are needed to confirm the findings.

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Research Article

Neutrophil/Lymphocytes Ratio and Haemoglobin Electrophoretic Pattern in an Undergraduate Student's Population Rivers State University, Port Harcourt, Nigeria

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Abstract: Neutrophil/lymphocyte ratio (NLR) is a very cheap and accurate method of accessing inflammation and is fast emerging as a prognostic biomarker in many diseases. This study determines the Neutrophil/lymphocyte ratio and haemoglobin electrophoretic patterns in an undergraduate student's population at Rivers State University, Port Harcourt, Nigeria. One hundred and fifty (150) undergraduate students aged between 17 and 30 years old were recruited for the study. Five millimeters (5ml) of venous blood was collected from each participants into ethylene diamine tetraacetic acid (EDTA) vacutainer bottle for the determination of haemoglobin genotype using cellulose acetate electrophoresis method while the neutrophil/lymphocyte ratio was calculated from neutrophil and lymphocyte values obtained from BC 5000 Mindray Hematology Auto-Analyzer. The results obtained showed that the mean±SD value of Neutrophil/Lymphocyte ratio was 1.21 ± 0.07 for male and 1.14 ± 0.06 for female participants with both within normal reference ranges and with no significant difference (p=0.4692). 100 (66.7%) subjects had haemoglobin genotype AA (HbAA) out of which 48 (32%) male, 52 (34.7%) female while 50 (33.3%) participants had haemoglobin genotype AS (HbAS) of which 24 (16%) male, 26 (17.3%) female. No haemoglobin genotype SS/SC (HbSS/HbSC) traits were seen in the study population. Furthermore, results also showed that haemoglobin genotype and sex had no effects on the neutrophil/lymphocyte ratio (p=0.05). This study shows a 66.7%, 33.3%, and 0% expression for HbAA, HbAS, and HbSS/HbSC, respectively, and that the Neutrophil/Lymphocyte ratio is within the normal reference range. Further studies to include other haemoglobin variants such as haemoglobin SS (HbSS) and haemoglobin SC (HbSC) is recommended.

Keywords: Neutrophil/Lymphocytes Ratio, Haemoglobin Electrophoretic patterns, Cellulose Acetate Electrophoresis Method.

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1. INTRODUCTION

Inflammatory activities occurring invivo constitutes normal immune defense mechanism in virtually all apparently healthy individuals. The neutrophil-to-lymphocyte ratio (NLR) in peripheral blood is an assay that strikes a balance between systemic inflammation and immunity and is thus an emerging prognostic biomarker in many diseases (1). The neutrophil-to-lymphocyte ratio (NLR) also serve as a biomarker connecting two part of the immune system; the innate and adaptive immunity, both mediated by the neutrophil and lymphocytes respectively. It is calculated as a simple ratio between the neutrophil and lymphocyte counts measured in peripheral blood (1).

Neutrophils are granulated cells that function as the first line of host immune response against invading pathogens through different mechanisms, which includes; chemotaxis, phagocytosis, release of reactive oxygen species (ROS), granular proteins, and the

production/liberation of cytokines (2). They also actively partake in adaptive immunity by playing an important regulatory role as main effector cells during the systemic inflammatory response (SIRS). Neutrophil as a major regulator of innate immunity, recruits, activates, and programs other immune cells and secretes an array of proinflammatory and immunomodulatory cytokines/chemokines capable of enhancing and advancing the effector function of other immune cells such as B cells, NK (Natural killer) cells, dendritic cells, CD4/CD8 cells (3).

Lymphocytes exist in different forms such as B cells; T cells, CD4-positive, CD4/CD8-negative or CD8-positive; natural killer T cells and are mainly responsible for adaptive immunity, providing an antigen-specific response regulated by the major histocompatibility complex (MHC) class I (4). Lymphocyte activity is involved in the host's response to viruses, tumor cells, atopy, and in the systemic inflammation response (4).

Haemoglobin electrophoretic patterns are the genotypic expression of haemoglobin that include both normal homozygous forms (HbAA) and abnormal heterozygous forms (HbSS, HbSC, HbCC, etc). The variant HbSC is formed by the replacement of glutamic acid with lysine at the 6th position of the β-globin chain while HbSS is formed by the replacement of glutamic acid with valine at the 6th position of the β-globin chain of the molecule (5,6,7). There are six major haemoglobin electrophoretic patterns inherited in the homozygous state (HbAA, HbCC, and HbSS) or heterozygous state (HbAS, HbAC, and HbSC) (8,9,10). The inheritance of HbS from both parents results in a homozygous state (HbSS) known as sickle cell anaemia/disease The inheritance of HbS from one parent and HbA from the other leads to a heterozygous state (HbAS) which is known as sickle cell trait (SCT) (8,11). Subjects with HbSS gene trait are easily prone to anaemia due to destruction of red blood cell by various mechanism that decrease red cell production, increase red cell destruction and ineffective red cell production (12). Management of the disease associated with heterozygous state of haemoglobin S (HbSS) are usually expensive and often not affordable by the poor as most drugs used in its management are insufficiently ineffective, expensive and toxic to cell (13)

Researches have shown that there is an isolated rise in neutrophil count and consequently an elevated neutrophil/lymphocyte ratio in several conditions including; bacteria or fungal infection (14,15,16) atherosclerosis (17) all of which are common features with haemoglobin SS genotype. This is because the early hyperdynamic phase of infection is characterized by a proinflammatory state, mediated by neutrophils and other inflammatory cells (14). Thus, NLR is often characterized by an increase in neutrophils and a decline in lymphocytes. Lower NLR is usually associated with favorable prognostic factors in every field of application, mirroring a preserved immune balance (18). This study is aimed at determining Neutrophil/Lymphocytes ratio and electrophoretic pattern in apparently healthy undergraduate student of Rivers State University, Port Harcourt Nigeria.

2. MATERIALS AND METHOD

2.1 Study Design/population

This cross-sectional study was aimed at determining the Neutrophil/Lymphocyte ratio and Haemoglobin Electrophoretic patterns in apparently healthy students in Rivers State University. The study was carried out in August-November 2022 with a total of one hundred and fifty (150) apparently healthy male and female participants aged between 16 to 45 years recruited through a well-structured questionnaire.

2.2 Sample Collection, Transportation, Processing and Preservation

Five (5) millilitres (ml) of venous blood sample were collected from each participants through venepuncture techniques into ethylene diamine tetraacetic acid (EDTA) vacutainer bottle and transported under recommended condition to the laboratory for analysis.

2.3 Methodology

Estimation of Neutrophil, Lymphocyte count was carried using BC 5000 Mindray Hematology Auto-Analyzer and neutrophil/lymphocyte ratio calculated. Haemoglobin

electrophoretic pattern was carried out using cellulose acetate electrophoresis method under an electric current and at an alkaline pH (8.4 - 8.6).

2.4 Calculation of Neutrophil/Lymphocyte Ratio

Neutrophil/lymphocyte ratio was calculated by dividing absolutes values of neutrophil and lymphocyte count estimation from full blood count haematology autoanalysers. Although, NLR can also be calculated from full blood count autoanalysers when values of neutrophil and lymphocyte are presented in percentage. This was done by respective calculation and multiplying neutrophil and lymphocyte values by white blood cell count and dividing by 100 and then dividing the results of neutrophil by lymphocytes.

2.5 Data Analysis

Data was statistically analyzed using Statistical package for Social Sciences (SPSS) version 23 and results presented in tables.

3. RESULTS

3.1 Demographic Data of Studied Subjects

Table 3.1 shows a total of one hundred and fifty (150) subjects were enrolled for the study, comprising of seventy-six (76) males and seventy-four (74) females participants aged between 17-30years.

Table 3.1: Demographic Data of Studied Participants

Parameters	*Frequency (%)*
Age range in years	17-30
Male	76(50.7%)
Female	74(49.3%)
Total	150

3.2 Percentage Distribution of Haemoglobin Genotype in Studied Participants

Result in the study shows that out of the total study population of 150 subjects, 100 (66.7%) participants were haemoglobin genotype A (homozygous A (HbAA) of which 48 (32%) were male and 52 (34.7%) were females. 50 (33.3%) of the studied participants were haemoglobin genotype AS (heterozygous AS (HbAS) of which 24 (16%) were male and 26 (17.3%) females as shown in table 3.2.

Table 3.2: Percentage Distribution of Haemoglobin Genotype in Studied Participants

Genotype	*Frequency (%)*
Haemoglobin A (HbAA)	
Male	48 (32%)
Female	52 (34.7%)
Total	100 (66.7%)
Haemoglobin AS (HbAS)	

Male	24 (16%)
Female	26 (17.3%)
Total	50 (33.3%)

3.3 Result of Neutrophil, Lymphocytes and Neutrophil/Lymphocyte Ratio of Studied Participants

Table 3.3 shows the mean±SD values of Neutrophil, Lymphocyte and Neutrophil/Lymphocyte Ratio in female participants as 46.22 ± 4.91(%) (p=0.6373), 44.09 ± 4.56 (%) (p=0.5745) and 1.14 ± 0.06 (p=0.4692) respectively. The mean±SD values of neutrophil, lymphocyte and neutrophil/lymphocyte ratio in male participants were 47.02 ± 5.85(%) (p=0.6373), 43.22 ± 4.37(%) (p= 0.5745) and 1.21 ± 0.07 (p=0.4692).

Table 3.3: Result of Neutrophil, Lymphocytes and Neutrophil/Lymphocyte Ratio of Studied Participants

Parameter	*Male (n=76)*	*Female (n=74)*	*P value*	*Remark*
Neutrophil (%)	46.22 ± 4.91	47.02 ± 5.85	0.6373	NS
Lymphocyte (%)	44.09 ± 4.56	43.22 ± 4.37	0.5745	NS
NLR	1.21 ± 0.07	1.14 ± 0.06	0.4692	NS

KEY: *n= number of participants, NLR=Neutrophil/Lymphocyte Ratio, NS= Not Significant when compared at p<0.05*

3.4 Effect of Haemoglobin Genotype on Neutrophil, Lymphocyte and Neutrophil/Lymphocyte Ratio

Table 3.4 shows the mean±SD values Neutrophil, Lymphocyte and Neutrophil/lymphocyte ratio in participants with haemoglobin AA (HbAA) as 46.65 ± 5.27(%) (p=0.9585), 44.05 ± 4.10 (%) (p=0.4690), and 1.16 ± 0.05 (p=0.6057) respectively. Participants with haemoglobin AS (HbAS) had mean±SD values of neutrophil, lymphocyte and neutrophil/lymphocyte ratio as 46.56 ± 5.66(%) (p=0.9585), 42.86 ± 5.13 (%) (p=0.4690), 1.21 ± 0.09 (p=0.6057) respectively.

Table 3.4 Effects of Haemoglobin Genotype on Neutrophil, Lymphocyte, Neutrophil/Lymphocyte Ratio

Parameters	*HbAA (n=100)*	*HbAS (n=50)*	*P value*	*Remark*
Neutrophil (%)	46.65 ± 5.27	46.56 ± 5.66	0.9585	NS
Lymphocyte (%)	44.05 ± 4.10	42.86 ± 5.13	0.4690	NS
NLR	1.16 ± 0.05	1.21 ± 0.09	0.6057	NS

KEY: *NLR=Neutrophil/Lymphocyte Ratio, n= number of participants, HbAA=haemoglobin genotype AA, HbAS=haemoglobin genotype AS, NS= Not Significant when compared at p<0.05*

4. DISCUSSION

The Neutrophil/lymphocyte ratio is an important haematological parameter derived by dividing absolute values of neutrophils by lymphocyte. It establishes the balance between systemic inflammation and immunity and is a rising prognostic biomarker in many diseases (19). This study was carried out to determine the Neutrophil/Lymphocyte ratio and

haemoglobin electrophoretic patterns in the apparently healthy undergraduate student population of Rivers State University.

Results for neutrophil/lymphocyte ratio showed that both male and female participants had NLR values all within established normal reference ranges. The findings in this study are deviant from the study of Alagbe and Olaniyi (20), who recorded significantly higher NLR values in subjects with HbSS compared to HbAA, and Beatrice *et al.* (21), who recorded lower values for NLR while assessing the effect of cART on neutrophil/lymphocyte ratio in HIV positive patients initiating antiretroviral therapy.

The finding in this study, however, is not surprising since there was no sickle cell haemoglobin genotype discovered among the participants in the study, which could have been a predisposing factor to inflammation and thus triggered elevated or decreased NLR values in the study population. It is known that sickle cell anaemia has always focused on the primary genetic defect, the abnormal sickle haemoglobin that polymerizes when deoxygenated. This polymerization within the red cell is capable of causing deformability of the cell and consequently resulting in the cell becoming rigid, obstructing blood flow. Obstruction of blood flow will trickle down to acute and/or chronic tissue damage due to poor perfusion of the cell.

Furthermore, the Neutrophil/lymphocyte ratio as a cheap assessment method of inflammation is somewhat more stable and not easily influenced by physiological, pathological, or stressful events known to influence neutrophil and platelet counts and activities. Therefore, since all participants in this study were apparently healthy, the triggers of inflammation that could have caused alterations in neutrophil/lymphocytes ratio are not present, and thus, the results observed in the study.

In this study, 100 (66.7%) participants comprising of 52(34.7%) male and 48(32%) females expressed the homozygous haemoglobin genotype AA (HbAA) while 50 (33.3%) comprising of 24 (16%) male and 26 (17.3%) females expressed the heterozygous haemoglobin genotype form AS (HbAS). No HbSS, HbAC and HbSC traits was seen in the study population. This finding slightly agrees with the findings of Erhabor *et al.* (22) who reported a 69.1% expression, Abdulrahaman *et al.* (7) who reported 70% expression of HbAA, Moses *et al.* (23) with 73.9% HbA and 26.1% HbAS in their study of pregnant women attending the antenatal clinic in Plateau State Specialist Hospital; Umoh *et al.* (24) who found out a 78.7% HbAA, 19.6% HbAS, 1.5% HbSS, 0.2% HbAC and 0.04% HbSC in their five (5) year retrospective study on haemoglobin genotypes as an implication for reproductive health in Uyo, Nigeria. The finding in this research is also within the normal reference range reported in blacks and in tandem with the reports of Abdulrahaman *et al.* (7)

From the findings in this research, it could be inferred that the HbAA is the most prevalent haemoglobin genotype among students of Rivers State University and this high percentage expression of HbAA, average prevalence of HbAS and no HbSS or HbSC can be attributed to the genes expressed in the population, high level of awareness and sensitization on the part of parents of the students on the negative social economic implications of haemoglobin genotype especially the HbSS on the health and wellbeing of their children. Also, the zero frequencies of HbSS observed in this study is a possible indication that the sickle cell gene trait in Port Harcourt is gradually reducing due to increased awareness, pre-marital counselling, increased awareness and knowledge of the devastating socio-economic implications and complications of the disease associated with HbSS gene. The absence and decrease prevalence in the HbSS and HbAS traits might also be attributed to the improved and active program for prenatal screening and diagnosis among pregnant women in Port Harcourt, Nigeria.

There was no statistically significant difference in the Neutrophil/Lymphocytes values in haemoglobin genotype AA (HbAA) compared to haemoglobin genotype AS (HbAS) ($p=0.6057$). This indicates that haemoglobin genotype have no significant effects on neutrophil/lymphocytes ratio. This could be because there was no haemoglobin genotype SS and other abnormal variants which are highly connected with inflammatory processes. It is known that subjects with HbSS gene trait are easily prone to anaemia due to the destruction of red

blood cells by various mechanism that decrease red cell production, increase red cell destruction and ineffective red cell production. Fragment of red cell has ability to stimulate immune response capable of increasing neutrophil and lymphocyte count in peripheral blood.

Although Neutrophil/Lymphocytes values were slightly elevated in males compared to female participants, it shows no statistically significant difference (p=0.4692) indicating that sex/gender have no significant effects on neutrophil/lymphocytes ratio. This could be because both the male and female participants had no condition or disease that affected or was capable of triggering the production of neutrophil/lymphocyte above normal reference values.

5. CONCLUSION

This study has revealed that haemoglobin genotype AA is the most prevalent genotype among the study population. Neutrophil/lymphocyte ratio of participants is within the normal reference range, and the haemoglobin genotype and sex have no effect on the neutrophil/lymphocyte ratio. Further studies to include other haemoglobin variants, such as haemoglobin SS (HbSS) and haemoglobin SC (HbSC), is recommended.

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Comparative Efficacy of Levofloxacin Versus Amoxycillin/Clavulanic Acid Combined with Azithromycin in Treatment of Community-Acquired Pneumonia

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Abstract

Background: Community-acquired pneumonia (CAP) is an important cause of mortality and morbidity worldwide. Early initiation of antibiotics is highly recommended. In most CAP cases, multiple drug options are increasingly becoming available, but there is often a lack of evidence that allows for a direct comparison of the efficacy of one drug versus another.
Aim: The main objective was to compare treatment outcomes using oral levofloxacin alone and combined azithromycin and amoxicillin/Clavulanic acid in outpatient treatment of Community-acquired pneumonia.
Methods: This study was a prospective longitudinal design. Patients diagnosed with CAP were randomly assigned to first and second treatment groups. Community-acquired pneumonia was diagnosed according to America Thoracic Society criteria. The sample size of 78 was arrived at by Yamane Taro (1967) formula. Every patient diagnosed and treated in the outpatient department who gave written consent to participate was enrolled in the study and randomly assigned to one of the treatment groups. Minors below 18 years were excluded from the study. Data were analysed using SPSS for Windows version 26. An independent t-test compared the effectiveness of the two treatment groups. Changes in white blood cell count during the follow-up visits were done using a chi-square test. A p-value of <0.05 was considered statistically significant.
Results. The majority, 33(50%) of the patients, were aged between 21 and 29 years, and over sixty percent, 42(63.6%) of participants were females. Of all the participants, 66(100%) had a cough and chest pain, 57(86.4%) had crackles, and about ten percent, 6(9.1%) had difficulty breathing at the time of admission into the study. About 29(43.9%) of patients had a fever at baseline, and 14(21.2%) had a respiratory rate between 16 and 29 breaths per minute at baseline. A combination of azithromycin and amoxycillin/clavulanic acid was associated with statistically significant faster resolution of chest pains and cough (mean 1.7 and 3.14 days, respectively) compared to levofloxacin group (mean 2.21 and 3.71 days, respectively) in patients who had community-acquired pneumonia (p=0.009. There was no difference in fever resolution, time to crackles subsidence, resolution of difficulty in breathing, and change in white blood cell count in participants in the two treatment groups.
Conclusions: Azithromycin combined with amoxycillin/clavulanic acid reduced chest pain in 1.70 days (SD=0.618) compared to levofloxacin alone (2.21 days, SD=1.204) (p=0.009). Azithromycin combined with amoxycillin/clavulanic acid reduced cough in 3.14 days (SD=0.789) versus levofloxacin alone (3.70 days, SD=0.588) (p=0.014). Hence, the azithromycin plus amoxycillin/clavulanic acid combination was found to be superior for managing CAP.

Keywords: community acquired pneumonia, CAP, Levofloxacin, Azithromycin, amoxycillin/clavulanic acid

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Introduction

Community-acquired pneumonia (CAP) is a type of pneumonia that is contracted outside of a hospital or other medical facility (1,2) characterised by inflammation of the lung parenchyma (3). Risk factors for CAP can be modifiable, such as smoking, or non-modifiable, such as inherited functional impairment of the lungs (4,5). Community-acquired pneumonia is a severe health issue that poses a significant threat to global healthcare systems as the primary cause of mortality among infectious illnesses (6,7).

Epidemiological studies in Kenya have demonstrated that viruses—particularly influenza viruses—were often detected in CAP patients and the underlying conditions, like HIV and cardiovascular diseases, among others, were comparable to those reported in high-resource areas, in contrast to other studies from sub-Saharan Africa (8). This suggests that the double burden of infectious and noncommunicable diseases is a growing cause for concern.

Community-acquired pneumonia may arise from diverse pathogens, encompassing a broad spectrum of bacterial agents. The term "core respiratory pathogens" describes the bacteria and viruses that are believed to be the most likely cause of pneumonia acquired in the community in all cases (9). Individuals with dual bacterial and viral infection have double the risk of mortality compared to patients without dual infection, even though viral pneumonia is a self-limiting illness (10). Bacterial pathogens implicated in CAP vary with geographic distribution and host characteristics (7). The most often found pathogen is Streptococcus pneumoniae (8.2%), followed by Pseudomonas aeruginosa (4.1%) and Klebsiella pneumoniae (3.4%) (11). Due to insufficient etiological data and resources and the unavailability of microbiological tests, identifying causative agents in resource-scarce settings like those in primary care centres in Kenya remains challenging. Hence, empirical antibiotic therapy is frequently used to manage the condition. Moreover, empirical antibiotic therapy is often effective, and thus, microbiologic testing for bacterial aetiology is generally not indicated for the majority of patients receiving care in ambulatory settings (9,12).

The key factors of the antibiotic class and mode of administration include age, comorbidities, and disease severity(13). Adults who present with suspected CAP get empirical antimicrobial chemotherapy in compliance with relevant national guidelines (12,13). For previously healthy patients who have not taken any antibiotics in the three months before presentation, the 2019 American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) both advocate monotherapy with macrolides or doxycycline in outpatient settings. For individuals with CAP and recent antibiotic use or comorbidity, a combination of an anti-pneumococcal beta-lactam like amoxycillin and a macrolide like an azithromycin or a respiratory fluoroquinolone like levofloxacin is advised (14,15)

However, there are a growing number of pharmacological alternatives as many antibiotics are available. However, there is a lack of clinical data regarding the efficacy of different antibiotics in managing CAP in Kenya. However, decision-making in clinical practice requires knowledge of the relative efficacy of different antibiotics or drugs (14,16). The wrong choice of empirical antibiotic therapy not only poses health risks due to poor outcomes but may also contribute to rising antibiotic resistance in the region. Given the challenge posed by such multiple drugs available in the treatment of CAP, this study compared the effectiveness of oral levofloxacin when used alone and amoxicillin/clavulanic acid combined with azithromycin in the treatment of CAP in the outpatient setting for patients with comorbidities or who have been exposed to antibiotics within the last three months.

Objective

To compare the effectiveness of levofloxacin alone versus combined azithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired pneumonia

Methods and Study Design

The study utilised a prospective longitudinal study design. Longitudinal designs involve repeated observation of the same participants to follow change over time. In the current study, patients diagnosed with community-acquired pneumonia were allocated to one of the usual treatment groups and observed for five days at intervals (Figure 1). The study was conducted between March 6, 2022, and December 18, 2022, at St Monica Hospital Kisumu, Kenya.

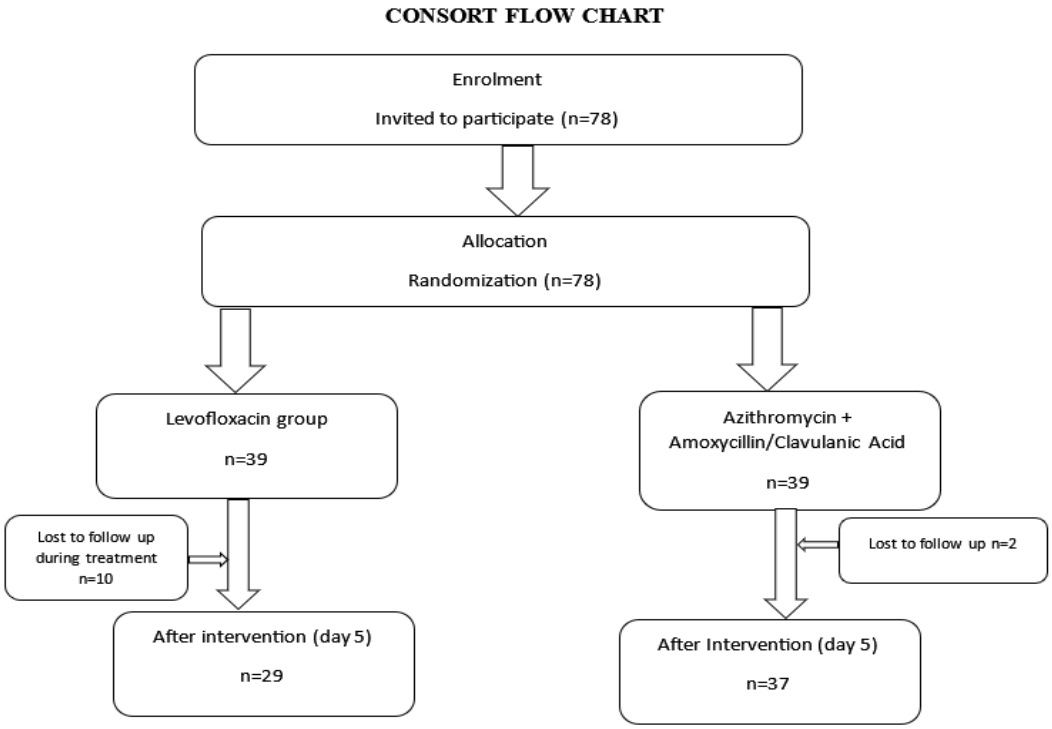

Figure 1: Consort flow chart. Seventy-eight participants were enrolled in the study and randomly allocated to the levofloxacin group or combined azithromycin and amoxycillin/clavulanic acid group, so each group had 38 participants. 10 participants in the levofloxacin group and 2 participants in the combined azithromycin and amoxycillin/clavulanic acid group were lost to follow-up, respectively.

This design was chosen to allow for a comparison of the efficacy of oral levofloxacin alone versus oral azithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired pneumonia in patients who were observed at intervals during treatment. These drugs are already in use, and there is no new drug involved.

Participants were observed on days 1, 3, and 5. The patients' information on clinical parameters was gathered. The change in clinical parameters of patients during the observation was used to determine effectiveness. The clinical parameters in the study included fever, cough, chest pain, shortness of breath, physical findings of crackles, and white blood cell count. A drug was considered effective if taking it resulted in the resolution of clinical parameters at the end of the treatment period.

Participants

The participants consisted of patients diagnosed with community-acquired pneumonia at St Monica Hospital Kisumu, Kenya, between March 2022 and December 2022.

Community-acquired pneumonia was diagnosed according to **America Thoracic Society (ATS) criteria** in which signs and symptoms of pneumonia included at least two of the following:

a) Fever (axillary temperature > 37.5˚C)

b) Cough for less than 14 days

c) Chest pain

d) Shortness of breath

e) Physical findings of consolidation

f) White blood cell count >15000/µl or <5000/µl

g) Chest x-ray showing evidence of lung infection (pulmonary opacity).

Eligibility criteria

a) Presentation to the Outpatient Department with probable community-acquired pneumonia.

b) Age between 18yrs and above

c) Smokes or used antibiotics for comorbidity within the last 3months

d) Written consent has been obtained from the patient/guardian

e) Parent or legal guardian is willing to allow the child to comply with the protocol and particularly to provide blood samples.

Interventions

The participants were put in one of the two intervention groups: Group 1: Levofloxacin group and Group 2: Azithromycin + Amoxycillin/Clavulanic acid group. In group 1, participants were given oral levofloxacin 500mg twice daily for five days. In group 2, participants were given azithromycin 500mg once daily for 3 days and amoxycillin/clavulanic acid 500mg/125mg twice daily for 5 days.

Outcomes

The main outcomes in the current study were the number of patients whose symptoms and clinical parameters (temperature, respiratory rate, white blood cell count) changed after the intervention. The primary outcomes included the resolution of cough, chest pain, and fever. The secondary outcomes included a change in white blood cell (WBC) count and a change in respiratory rate.

Sample size

A total of 78 participants were recruited for the study.

Randomisation

Every patient diagnosed and treated in the outpatient department who gave written consent to participate was enrolled in the study and randomly assigned to one of the treatment groups. Minors below 18 years were excluded from the study. With the help of research assistants, the researcher enrolled every eligible participant as they came until 78 participants were enrolled in the study**.** Patients were randomly assigned to each treatment group to get 39 patients in each group.

Blinding

The current study was unblinded. All participants knew the drugs they were using for the treatment of community-acquired pneumonia.

Statistical analysis methods

Data were analysed using SPSS for Windows version 26. A comparison of effectiveness between the two treatment groups was done using an independent t-test. Changes in white blood cell count during the follow-up visits were done using a chi-square test. P value of <0.05 was considered statistically significant.

Ethical consideration

This study is a registered trial with trial number PACTR202308507206446 and was licensed by the National Commission for Science, Innovation, and Technology via license number NACOSTI/P/22/15077. Jaramogi Oginga Odinga University of Science and Technology Board of Postgraduate Studies approved this study vide approval letter reference number: 152/4071/2017. This study was approved by the Baraton University ethics committee with reference number B0734432021. Each patient was explained about the study, including benefits and risks. Those who accepted were given the consent form to sign written informed consent form. Minors (<18 years) were excluded from the study. The researcher kept All information from the study in a safe box. The participants were anonymised; thus, no patient identifiers were collected during and after the study. The researcher provided adverse events notification form in case a patient experienced allergies or reactions to the drugs in the study. No adverse event was documented at the end of the study.

Results

Demographic characteristics of respondents

The patients were categorised into two treatment groups, i.e., oral levofloxacin-based group, 29(43.9%) and dual Azithromycin and Amoxicillin/Clavulanic acid-based group, 37(56.1%) and compared during the study. In relation to participant age, the majority, 33(50%) of the patients, were aged between 21- 29 years, and over sixty percent, 42(63.6%) of participants, were females. Of all the participants, 66(100%) had a cough and chest pain, 57(86.4%) had crackles, and about ten percent, 6(9.1%) had difficulty breathing at the time of admission into the study. About 29(43.9%) of patients had a fever at baseline, and 14(21.2%) had a respiratory rate between 16 and 29 breaths per minute at baseline. **(Table 1)**

Table 1: Demographic detail and Baseline Characteristics of the patients

Variable	**Total (N=66, %)**	**Groups**	
		Oral Levofloxacin	**Dual Azithromycin Plus Amoxicillin/Clavulanic acid**
Age Category(years)			
<20	4(6.1%)	1(25%)	3(75%)
21-29	33(50%)	18(54.5%)	15(45.5%)
30-39	13(19.7%)	8(61.5%)	5(38.5%)
>40	16(24.2%)	10(62.5%)	6(37.5%)
Gender			
Male	24(36.4%)	14(58.3%)	10(41.7%)
Female	42(63.6%)	23(54.8%)	19(45.2%)
Fever (Axillary temperature)			

Yes	29(43.9%)	16(55.2%)	13(44.8%)
No	37(56.1%)	33(64.7%)	16(43.2%)
Difficulty in breathing			
Yes	6(9.1%)	3(50%)	3(50%)
No	60(90.9%)	34(56.7%)	26(43.3%)
Chest Pain			
Yes	66(100%)	37(66.1%)	29(43.9%)
Crackles			
Yes	57(86.4%)	34(59.6%)	23(40.4%)
No	9(13.6%)	3(33.3%)	6(66.7%)
Respiratory Rate(breaths/minute)			
16-20	52(78.8%)	30(57.7%)	22(42.3%)
21-29	14(21.2%)	7(50%)	7(50%)
WBC at first visit (x10^9/µL)			
Visit 1	10.1±4.29	10.94± 2.93	9.03± 5.45
<6	7(10.6%)	6(85.7%)	1(14.3%)
6.1-14.9	51(77.3%)	20(39.2%)	31(60.8%)
>15	8(12.1%)	3(37.5%)	5(62.5%)
Cough at first visit			
Yes	66(100%)	29(43.9%)	37(56.1%)

Comparison of the effectiveness of Oral Levofloxacin and dual Oral Azithromycin and Amoxicillin/Clavulanic Acid in the treatment of CAP.

Comparison of time to resolution of CAP as per WBC Count between the two treatment groups

At initial visit, about 8(12.1%) had elevated WBC count (>15x 10^9/µL) and about ten percent, 7(10.6%) had low WBC count (<6x 10^9/µL). At visits two and three, after the treatment change, the WBC count was significantly associated with the treatment group the patient belonged to ($p<0.05$). At visit 2, 3(75%) of patients had elevated WBCs in the oral Levofloxacin group compared to only 1(25%) in the dual azithromycin amoxicillin/clavulanic acid group. At visit 3, one patient had elevated WBCs in the oral levofloxacin group, whereas none had elevated WBCs in the dual Azithromycin and Amoxicillin/clavulanic acid group. **(Table 2)**

Table 2: WBC Count during the first visit and Subsequent visits.

Variable	Groups	P Value

	Total (N=66, %)	Oral Levofloxacin	Dual Azithromycin and Amoxicillin/Clavulanic acid	
WBC at Visit 1(x10^9/µL)				
<6	7(10.6%)	6(85.7%)	1(14.3%)	0.062
6.1-14.9	51(77.3%)	20(39.2%)	31(60.8%)	
>15	8(12.1%)	3(37.5%)	5(62.5%)	
WBC at Visit 2(x10^9/µL)				
<6	12(18.2%)	10(83.3%)	2(16.7%)	0.002
6.1-14.9	50(75.8%)	16(32%)	34(75.8%)	
>15	4(6.1%)	3(75%)	1(25%)	
WBC at Visit 3(x10^9/µL)				
<6	19(28.8%)	13(68.4%)	6(31.6%)	0.016
6.1-14.9	46(69.7%)	15(32.6%)	31(67.4%)	
>15	1(1.5%)	1(100%)	0%	

P Values yielded by chi-square test of association

Comparison of time to resolution of symptoms

There was a difference in the mean time to resolution of cough and chest pain between the two treatment groups. The mean time to resolution of chest pain was 1.7 days in the dual azithromycin and amoxicillin /clavulanic acid group as compared to 2.21 days in oral levofloxacin (p=0.009). The mean time to resolution of cough was 3.71 days in the oral Levofloxacin group as compared to 3.14 days in the dual Azithromycin and Amoxicillin/clavulanic acid(p=0.014). There was no difference in the meantime to fever resolution, time to crackles subsidence, time to resolution of difficulty in breathing, or change in WBC count at visits 2 and 3 in oral levofloxacin compared to dual Azithromycin and Amoxicillin/clavulanic acid (p>0.05). (**Table 3)**

Table 3: Comparison of effectiveness of oral Levofloxacin and the dual Azithromycin and Amoxicillin/Clavulanic acid based on time to resolution of symptoms

	Oral Levofloxacin Group (Mean±SD)	Dual Azithromycin and Amoxicillin/Clavulanic acid Group (Mean±SD)	Mean Difference (95% CI)	P value
Time to Fever resolution(days)	0.88±1.204	1.0±1.815	-0.125(-1.216-0.966)	0.817
Time to Chest pain resolution(days)	2.21±0.902	1.70±0.618	0.504(0.130-0.878)	**0.009**

Time to Crackles subsidence(days)	1.00±0.853	1.11±0.583	-0.114(-0.491-0.263)	0.546
Time to difficulty in Breathing resolution(days)	0.10±0.310	0.11±0.393	-0.005(-0.183-0.173)	0.958
Time to Cough resolution by day 5	3.71±0.588	3.14±0.789	0.568(0.123-1.013)	**0.014**
Change in WBC count at visit 2	7.53±4.072	11.18±13.31	-3.654(-8.864-1.555)	0.166
Change in WBC count at visit 3	6.84±2.93	7.69±1.53	-0.855(-1.973-0.261)	0.131

P Value yielded by independent T-test

Discussions

In the current study, females made up the majority (42, 63.5%) of the participants who had community-acquired pneumonia. The results are contrary to other studies (17) which reported that males were affected more than females (36.5% versus 76%). It should be kept in mind that participants in such studies were both hospitalised and non-hospitalised, and studies have shown that males are more likely to be admitted than females (18). Participants aged 21 – 29 years were the majority (33, 50%). **(Table 1).** This finding was unexpected since, in the last decade, most studies (19,20) have indicated that old age (>65) is associated with an increased incidence of community-acquired pneumonia. One possibility could be the presence of underlying comorbidity among participants that predisposes the young age to community pneumonia, given that HIV infections are regarded as high in the setting of the study (21). Another possible explanation is that the study period (March to December) consisted of the winter season, which is often associated with sporadic respiratory infections (22). However, it should be kept in mind that this study did not delve into microbiological aspects of CAP diagnosis nor existing comorbidities among the participants.

All patients who presented had chest pains and coughs. **(Table 1).** Similar findings have been reported by (23,24). At the time of reporting to the hospital for treatment, most participants (37, 56%) did not have fever, 60 (96.9%) did not have difficulty breathing. Fever has been reported by other authors (24) to have a positive predictive value in 57% of viral infections. The results of the current study raise the possibility of mixed microbial infections among the participants. Although cough is common in CAP, studies such as(24) have reported that the viral aetiologies of CAP are less likely to cause productive cough. The current study did not emphasise productive versus nonproductive cough, and neither was a COVID-19 test required.

When examined, the majority (57, 86.4%) of the participants had crackles (24,25), and 52 (78.8%) had a normal respiratory rate (16 – 20). The study also found that most (51, 77.3%) had a normal white blood cell count at baseline versus 8, 12.1% who presented with white blood cell count >15*10^9/μL. Similar findings have been reported by other authors (23,24). The implication of this finding is that white blood count should not be relied upon as a marker in making a diagnosis of community-acquired pneumonia. Similar recommendations have been made in other studies (25).

There was a statistically significant difference between the two groups in days taken to resolve chest pain and cough. Chest pain resolved on average 1.70 days, SD=0.618 in azithromycin plus amoxicillin/clavulanic acid group versus levofloxacin group in which chest pain resolved in 2.21 days, SD=1.204 (p=0.009). Cough resolved on average 3.14 days, SD=0.709 for azithromycin plus amoxycillin/clavulanic acid group versus 3.71 days, SD=0.588 for levofloxacin group (p=0.014). There was no statistical difference between the combined azithromycin and amoxycillin/clavulanic acid versus levofloxacin group in relation to changes

in fever, crackles, difficulty in breathing and white blood cell count among the participants (p>0.05). **(Table 3**). Combining a beta-lactam/lactamase and a macrolide demonstrated better outcomes in the treatment of community-acquired pneumonia and appears to result in improved survival and, possibly, shorter hospital length of stay in the hospital (15,26) . A possible explanation would be that combination therapy provided a broader spectrum of antimicrobial activity and offered multiple mechanisms of action for better antimicrobial coverage (27). Given that all of the participants reported chest pains and cough when they presented to the hospital at the initial visit, the implication of the current findings is that a drug(s) that can resolve the most common symptoms fastest may be appropriate in the current setting.

Conclusions

Azithromycin combined with amoxycillin/clavulanic acid reduced chest pain in 1.70 days (SD=0.618) compared to levofloxacin alone (2.21days, SD=1.204) (p=0.009). Azithromycin combined with amoxycillin/clavulanic acid reduced cough in 3.14 days (SD=0.789) versus levofloxacin alone (3.70 days, SD=0.588) (p=0.014). There was no statistical difference between combined azithromycin and amoxycillin/clavulanic acid versus levofloxacin group in relation to change in fever, crackles, difficulty in breathing and white blood cell count among the participants with community-acquired pneumonia (p>0.05).

Recommendations for clinical practice

Based on these conclusions, the practitioners and policymakers should;

I. Prioritise the use of amoxycillin/clavulanic acid combined with azithromycin in treating community-acquired pneumonia in patients who have had previous antibiotic exposure within the last three months.

II. Not restrict the use of levofloxacin in patients who may benefit from treatment of community-acquired pneumonia, provided the possibility of tuberculosis has been ruled out.

To better understand the implications of the results in this study, future studies could address the optimal dosage for patients using the drugs in the current study.

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Original article

Adherence to Anti-seizure Drugs and Associated Factors among Children with Epilepsy in central Sudan

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Abstract:

Background: Epilepsies are the most common neurological disorder in children worldwide. They result in disability or even death. Adherence to anti-seizure drugs (ASDs) is challenging for children with epilepsies.

Methods: This cross-sectional descriptive study was conducted on 67 children with epilepsies age between (2-16 years of age) on follow up visits at neurology refer clinic at Wad Medani Pediatric Teaching Hospital; Central Sudan from February to July. 2022. Adherence to ASDs was measured using Morisky's Medication Adherence Scale eight – items (MMAS-8) translated to the local language. Descriptive analysis was conducted to calculate frequencies and percentages for categorical data, chi-square test for associated factors with adherence. A P-value of < 0.05 was considered statistically significant.

Results: Gender analysis showed that 36 (53.7%) of patients were males. Forty-eight (71.6%) had good adherence to their medications. Thirty-three (49.3%) had 1-12 seizures/year. Thirty-nine (58.2%) of participants had generalized seizures while 22 (32.8%) had focal seizures. Sixty-six (95.5%) of study patients on poly therapy had good adherences. Adherence was not found to be associated with sex, age, parental education, employment status, ASDs, duration of epilepsy, type of epilepsy, seizures frequency or monotherapy versus poly therapy (p value > 0.05).

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1. Introduction

Epilepsy is the most common neurological disorder in children. In Sudan epilepsy accounts for 1.6 annual mortality rates and 238.7 disability adjusted life years per 100 000 (1). Treatment of epilepsy with anti-seizure drugs (ASDs) for 2-5years is important to control convulsions, this requires good adherence to the medications (2). Medical adherence is generally defined as "the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider" (3). Adherence to ASDs is challenging for epileptic children (4).

Studies in children with epilepsy have reported adherence in 50–96.5% (3) and (5). Accurate assessment of adherence behavior is necessary for effective and efficient treatment

planning, and for ensuring that changes in health outcomes can be attributed to the recommended regimen (6)

2. Materials and Methods

Study Design:

Cross-sectional descriptive, hospital-based study design was used for the assessment of adherence of patients/ family members to ASDs

Study Area:

This study was conducted at Wad-Medani Pediatric Teaching Hospital; a tertiary hospital in Wad-Medani city the capital of Gezira State in Central Sudan. The patients and their families visit the outpatient refer clinic every month for regular follow up where the study was done. The study was conducted in the period from February/2022 to July/ 2022.

Study Population:

The subjects of the study were children with epilepsy (2–16 years) who had been visiting neurology refer clinic and their care givers. Total number of study sample was 67. Probability sampling (systematic random sampling) was used.

Inclusion criteria:

Children who received an epilepsy diagnosis and were prescribed one or more ASD/s; children age between 2 and 16 years; had no comorbid medical conditions requiring a daily medication, had no significant developmental disorders reported by their caregivers, and informed consent provided by the patient or family members. Exclusion criteria were refused consent and any criterion not included in inclusion criteria.

Data Collection method:

A patient was assigned an identification number, and then interview was done to older patients directly or to the care givers of younger patients who could not respond to the interview. Descriptive medical data (type of epilepsy, disease duration, prescribed ASDs, and seizure frequency) and demographic data (child age and gender) were collected from patient's card. Father employment status was collected directly from the family member during the interview.

Seizures were classified according to the International League Against Epilepsy classification (ILAE) (7)

Patients and/or caregivers were interviewed using eight-item Morisky Medication Adherence Scale (MMAS-8) sheet to assess the adherence to the ASD/s. MMAS-8 was translated to Arabic language to suit Sudanese patients/ caregivers (**Appendix A**). Each item was scored as either 0 (Yes) or 1 (No). The score of each item was then summed up to give a range of scores from 0 to 8. A score of >6–8 suggested that the patient had good adherence, while a score of ≤ 6 suggested that the patient had poor adherence.

Statistical analysis:

Collected data was entered into the statistical package of social sciences (SPSS) version 20 and descriptive analysis was conducted to calculate frequencies and percentages for categorical data, chi-square test for association. A P-value of < 0.05 was considered statistically significant in related tests.

3. Results

3.1. Socio-clinical demographic data:

Total number of patients/family members who were studied was 67. There were 36 (53.7%) of study patients were males and 31(46.3%) were females. There were 27 (40.3%) of patients were in age between 2-6 years, and 19 (28.4%) were between 12-16 years old. Exactly 64S (95.5%) of participants had their fathers employed. There were 33 (49.3%) of study

patients had 1-12 seizures/year, 18 (26.9%) were Seizure free for > 12 months, 10 (14.9%) had 2-4 seizures/month, 3 (4.5%) of had 1-7 seizures/ week, and 3 (4.5%) had daily seizures. There were 39 (58.2%) of participants had generalized seizures, 22 (32.8%) had focal seizures, 5 (7.5%) had myoclonic seizures, and 1 (1.5%) had unclassified seizures. Twenty-nine (43.5%) of study patients were prescribed sodium valproate, 18 (27%) were prescribed carbamazepine-IR, 7 (10.5%) were prescribed carbamazepine-CR, 6(9%) were prescribed levetiracetam and

the rest were prescribed polytherapy involved clonazepam as add on therapy. Exactly (76.1%) of study patients had seizure duration for > one year, 7 (10.4%) of study patients had duration of 5-8 months. Sixty (89.6%) of study patients were prescribed monotherapy. Table (1)

Table 1. This is a table of distribution of Study patients according to clinical demographic characteristics

Variable	Frequency	Percent %
Seizure frequency		
Seizure free for > 12 months	18	26.9%
1-12 seizures/ year	33	49.3%
2-4 seizures/ month	10	14.9%
1-7seizures / week	3	4.5%
Daily seizures	3	4.5%
Type of epilepsy		
Generalized	39	58.2%
Focal	22	32.8%
Myoclonic	5	7.5%
Not classified	1	1.5%
Prescribed ASDs		
Valproate	29	43.3%
Carbamazepine	25	37.3
Levetiracetam	6	9%
Other ASDs	7	10.4%
Duration of epilepsy		
1-4 months	4	6%
5-8 months	7	10.4%

9-12 months	5	7.5%
> One year	51	76.1%
Other		
Monotherapy	60	89.6%
Polytherapy	7	10.4%
Total		
	67	100%

3.2. Adherence to ASDs:

There were 48 (71.6%) of study patients had good adherence to ASDs, and 19 (28.4%) of patients had poor adherence to ASDs. Figure 1.

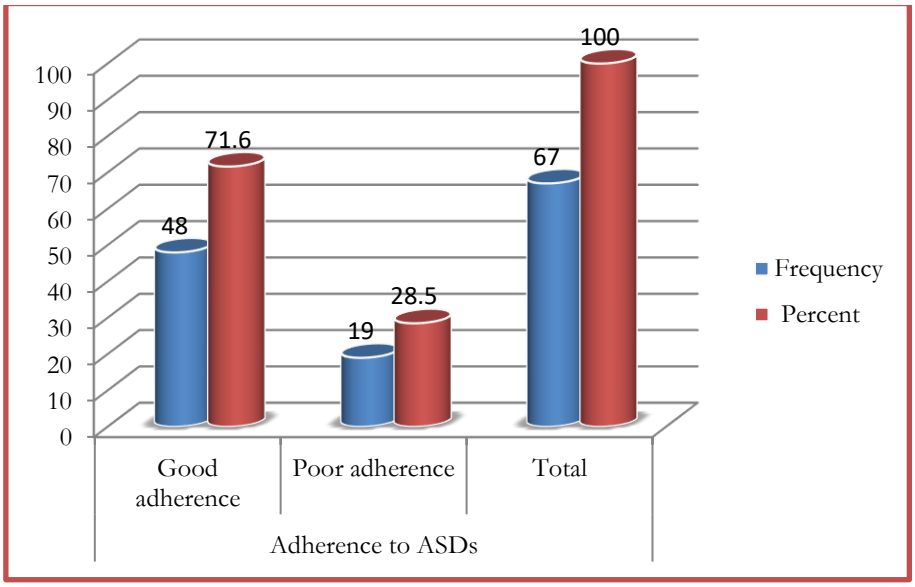

Figure 1. This is a figure of distribution of patients according to adherence to ASDs

3.3. Causes of poor adherence to ASDs:

There were 16 (23.9%) of factors were "forgot to take their ASDs", and 9 (13.4%) of causes were "did not take ASDs to cause other than forgetfulness". Table 2

Table 2. This is a table of distribution of patients according to causes of poor adherence

		Frequency	Percent
Causes of poor adher-ence	Forgot to take ASDs	16	23.9
	Did not take ASDs	9	13.4
	Cut back or stopped ASDs when felt worse	5	7.5

	did not take ASDs yesterday	1	1.5
	Felt hassled about sticking to ASDs plan	5	7.5
	Stopped ASDs when felt better	4	6.0
	How often had difficulty remembering to take ASDs(sometimes, usually, all the time)	5	7.5
	Total	45	67.2
	System	22	32.8
Total		67	100.0

3.4. Duration of epilepsy and adherence to ASDs:

There were 4 (57.1%) of the study patients with duration of 5-8 months had poor adherence, 4 (80.0%) , 3(75.0%) and 38 (74.5%) of the study patients with duration of 9-12 months, 1-4 months and > one year respectively had good adherence to ASDs. Table 3.

Table 3. This is a table of distribution of study patients according to adherence to ASDs and duration of epilepsy

Adherence to ASDs drug/s * Duration of epilepsy Crosstabulation							
			Duration of epilepsy				Total
			1-4 months	5-8 months	9-12 months	> one year	
Adherence to ASDs drug/s	Good adherence	Count	3	3	4	38	48
		% within Duration of epilepsy	75.0%	42.9%	80.0%	74.5%	71.6%
	Poor adherence	Count	1	4	1	13	19
		% within Duration of epilepsy	25.0%	57.1%	20.0%	25.5%	28.4%
Total		Count	4	7	5	51	67
		% within Duration of epilepsy	100.0%	100.0 %	100.0%	100.0 %	100.0 %

3.5. Monotherapy versus polytherapy and adherence to ASDs:

There were 18 (30%) of study patients who received monotherapy had poor adherence and 6(85.7%) of study patients who were prescribed polytherapy had good adherence. Table 4.

Table 4 This is a table of distribution of study patients according to adherence to ASDs and monotherapy versus polytherapy

Adherence to ASDs drug/s * Monotherapy versus polytherapy Crosstabulation					
			Monotherapy versus polytherapy		Total
			Monotherapy	Polytherapy	
Adherence to ASDs drug/s	Good adherence	Count	42	6	48
		% within Monotherapy versus polytherapy	70.0%	85.7%	71.6%
	Poor adherence	Count	18	1	19
		% within Monotherapy versus polytherapy	30.0%	14.3%	28.4%
Total		Count	60	7	67
		% within Monotherapy versus polytherapy	100.0%	100.0%	100.0%

3.6. Association tests for adherence (Chi-square test):

Adherence was not found to be associated with sex, age, parental education, employment status, ASDs, duration of epilepsy, type of epilepsy, seizures frequency, monotherapy or polytherapy (p-value > 0.05). Table 5

Table 5. This is a table of Chi-square test for association of socio-clinical variables and adherence

Variable	**Pearson chi-square test**		
	Value	df	Asymp.sig.(2-sided) (p-value)
Sex	0.432	2	0.511*
Age	2.06	1	0.357*
Parental education	2.92	3	0.404*
Employment status	1.24	1	0.265*
ASDs	7.07	8	0.528*
Duration of epilepsy	3.255	1	0.354*
Type of epilepsy	4.63	3	0.201*
Seizures frequency	2.857	4	0.582*

Monotherapy versus polytherapy	0.762	1	0.383*

4. Discussion

More than half of the study patients were males. That means epilepsy was more common in males than in females in our setting. This result agreed with a result from a study by (8) which showed male predominance (64.9%) and study conducted in Southwest Ethiopia (54.7%) (9).

Epilepsy was more common in young children than in older children in our setting. This result agreed with fact that the resolution of epilepsy occurs spontaneously when the brain develops with age advancing. Around half of the study patients had 1-12 seizures / year.

More than half of study patients were diagnosed with generalized seizures which were the most common type of epilepsy stated by a study (10). Another study from Sweden found that focal seizures alone or plus generalized seizures were more common (54.0%) (11). Focal epilepsy was also common in our setting but with fewer frequencies.

Near to three quarter of study patients had good adherence to their medications. This result is relatively good for poor setting like ours. Similar results of adherence (68.9%) was found in a study conducted in a developed country like Germany (12), and near to a result from a developing country like Uganda(79.5%) (13), but not similar to a result from a study conducted at Nigeria (44.8%) (14).

Valproate as ASD was the most commonly prescribed, followed by carbamazepine. Similar result was found by many studies, (15) from China and (50.5%) from Jordon (16). Levetiracetam as monotherapy was prescribed to a less extent despite that it is one of the safest ASD and involved in management of different types of epilepsy by international guidelines. In our setting; levetiracetam was not available as free.

General adherence was good in around three quarter of study patients. This result was better than the expected when taking in consideration the period during which the study was conducted (Covid-19 pandemic and the Sudanese revolution). Most of the causes for poor adherence stated by the patients/ family members were "forgot to take ASDs" and to less extent "did not take their medications to causes other than forgot". The later cause may be explained in our setting by financial problems that face the majority of the patients' care givers. Sometimes the patients and their family members come from far villages for follow up and for filling their prescriptions, this costs them money. Some ASDs specially syrups (like valproic acid and levetiracetam) are expensive and could not be afforded by the patients' care givers, and sometimes could be unavailable at all.

Small number of study patients and family members stated that they had no idea that ASDs should be taken regularly for long time to control seizures. This point should be explained clearly in the future by the health- care giver during counseling.

About three quarter of patients who were on valproate had a good adherence to it, most of patients who were prescribed CBZ had better adherence to controlled release CBZ than to immediate release CBZ. This may be due to better tolerability of controlled release form.

Most of the study patients were on monotherapy. Those who were on polytherapy had the higher percentage of adherence despite that other research found it to be of low percentage because of poor compliance (17, 18), The number of study patients who were prescribed polytherapy was small and therefore cannot be used to judge that adherence was better in this category of study patients.

Quarter or near to quarter of the study patients had poor adherence to ASDs. This was observed in different categories of epilepsy durations. Nonetheless, those with duration of

the disease (5-8) months, the adherence were poor in more than 50%. This result may be affected by the small number of study patients in this category.

Adherence was not found to be associated with any factors in our study. Other studies found it to be associated with age of patient, type of epilepsy, total household income, and source of drug information (5), age, the frequency of seizure, type of seizures, type of medication and the number of administered drug (4) presence of seizure attack in the past 3months and low family income (10)

5. Conclusions

Adherence to anti-seizure drugs was not as good as required. This study assessed adherence by subjective method, objective method is further needed to assess adherence to ASDs however. More efforts are needed to provide patients and their families with information about the importance of adherence to their medications, and to duration the government to supply the medications for free to patients.

6. Patents

Author Contributions: Conceptualization, investigation, methodology: Prof. Imad-Eldeen Mohammed Taj El, Prof. Haydar El Hady Babikir, and Dr. Ibrahim Osman M. Omer. Data curation, software, formal analysis, writing original draft and visualization: Dr. Salma Hassan Mohammed Eltahir. Resources (Patients): Prof. Haydar El Hady Babikir and Dr. Salma Hassan Mohammed Eltahir. Validation: Prof. ImadEldeen Mohammed Taj El Deen and Prof. Haydar El Hady Babikir. Writing-review and editing: Prof. ImadEldeen Mohammed Taj El Deen and Prof. Haydar El Hady Babikir.

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Institutional Review Board Statement: This study was conducted after it had been approved by the Ministry of Health Gezira state and Ethical Committee of University of Gezira before patients had been approached, recruited, and enrolled in the study. This article was a part of another study carried out by the same authors. So, ethical approval was taken for the whole study and it possessed the number: 5-22 on 22/2/2022; however, this article involved no experimental tests on humans or animals.

Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study."

Conflicts of Interest: "The authors declare no conflict of interest."

Appendix A

Arabic translated form of eight- item Moriskey Medication Adherence scale (MMAS-8)

	Yes نعم (0)	No لا (1)
1-do you sometimes forget to take medication? هل تنسى احيانا اخذ / اعطاء الدواء لطفلك؟		
2-people sometimes miss taking medications for reasons other than forgetting. Over the past 2 weeks, were there any days when you did not take your medication? **لايتناول الناس احيانا الدواء لاسباب اخرى غير النسيان. هل حدث في الاسبوعين الماضيين انك لم تاخذ / لم تعط طفلك الدواء في بعض الايام ؟**		
3-have you ever cut back or stopped taking medication without telling your doctor because you felt some worse when you took it? **هل حدث وان توقفت عن اخذ / اعطاء الدواء لطفلك بدون اخبار طبيبك بسبب الشعور بحال اسوء عند تناول الدواء؟**		
4-When you travel or leave home, do you sometimes forgot to bring up your medication? **هل تنسى احيانا اخذ دوائك/ دواء طفلك معك عندما تسافر او تغادر المنزل ؟**		
5-did you take all your medication yesterday? **هل اخذت كل ادويتك/ اعطيت طفلك كل ادويته بالامس؟**		
6-when you feel like your symptoms are under control, do you sometimes stop taking your medication? **هل تتوقف عن تناول ادويتك /عن اعطاء طفلك ادويته عندما تحس باختفاء اعراض المرض؟**		
7-taking medication every day is a real inconvenience for some patients.do you ever feel hassled about sticking to your medication plan? **اخذ الدواء يوميا يعتبر مصدر ازعاج حقيقي لبعض الناس. هل شعرت يوما بالضيق حيال خطة العلاج ؟**		
8-how often have you difficulty remembering to take all your medication? **كم عدد المرات التي وجدت فيها صعوبة في تناول /اعطاء الدواء لطفلك؟**		

Never /rarely…… **ابدا/ نادرا .....** Once in a while …… **مرة كل حين .....** Sometimes …….. **في بعض الاحيان .....** Usually …… **عادة.....** All the times ……. **كل الوقت.....**		
Score (0-8) **درجة (0-8)**		
Good Adherence(> 6-8)/ pooradherence (≤ 6)		

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Research article

Awareness And Utilization of Community-Based Health Insurance Schemes Among Residents of Rumuokwurusi, Obio/Akpor Local Government Area, Rivers State

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Abstract:

Community-based health insurance (CBHI) in a developing country such as ours aims at achieving universal health coverage, especially for those not financially capable of footing out-of-pocket medical bills. CBHI schemes can help communities manage healthcare costs and provide access to basic healthcare for rural settlers. This study aimed at assessing the awareness and utilisation of CBHI schemes in Obio/Akpor Local Government Area (LGA), Rivers State, Nigeria.

This was a descriptive cross-sectional study, employing the multistage probability sampling technique to select participants for the study. Semi-structured interview-er-administered questionnaires were designed for obtaining information from 250 respondents on the title. Data were analyzed on Excel spreadsheets, having been extrapolated from Google Forms, and results presented in frequency tables. The p-value was set at <0.05 where Chi-square was necessary.

Of the 250 respondents, 114 (45.6%) were aware of community-based health insurance, but only 86 (34.4%) were acquainted with the existence of Community-based health insurance schemes in Obio/Akpor LGA. Only 26 (10.4%) utilized Community-based Health Insurance Schemes.
Awareness and utilization of CBHI schemes in our study area are very low. Recommended strategies need to be addressed urgently to improve equity in access to health care services as well as effective financial risk protection.

Keywords: Awareness, Utilization, Community-Based Health Insurance, Obio/Akpor Local Government Area.

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1. Introduction

The availability of health insurance services is critical to healthcare financing, especially for resource-poor countries. The existence of community health insurance bridges tackles poor health-seeking behaviour and improves access to healthcare, one of the sustainable development goals (SDG) for universal health coverage. CBHI therefore eliminates barriers to healthcare due to catastrophic spending, and such schemes can help communities manage healthcare costs in low-income rural and informal sector workers.

Despite all the benefits of community-based health insurance, it has been observed that most Nigerians are either not sensitized to the idea of health insurance or have simply chosen to be apathetic to the concept. The bulk of this study is aimed at assessing the awareness, utilization and factors influencing the utilization of CBHI schemes among residents of Rumuokwurusi, Obio/Akpor Local Government Area (LGA), Rivers State, Nigeria.

Community-based health insurance schemes (CBHIS) are smaller groups of health insurance schemes that apply the principles of health insurance to the social context of communities, guided by what they prefer and based on their structures and arrangements(1). The goals of any form of health insurance include health equality, responsiveness of health systems to people's non-medical expectations and fairness in financial contribution(2). For community-based health insurance to achieve these goals, longevity and sustainability are important. The factors that could contribute to the sustainability of this scheme include; a high participation rate among target populations, which contributes to financial sustainability, which is a key factor that builds confidence in people to partake in the scheme. In addition, the behaviour of health care providers and household and community characteristics also play a role in sustainability(3).

The underutilization of community health insurance schemes is concerning, especially in Nigeria where its importance has been noted in previous research (4). The lack of an effective health insurance scheme has led to so many out-of-pocket bills, which further cripples the already bad economy of the country. In addition to that, it has led the citizens to lose faith in the healthcare system as they feel the hospitals are exploiting them due to the high cost of healthcare. As earlier mentioned, a high participation rate and increased resource mobilization are important for the sustainability of a health insurance scheme; however, in Nigeria, the majority of those registered under the health insurance scheme are people in the formal sector(5,6). This means that those who will truly benefit from this scheme (informal workers and low-income households) are not utilizing the health insurance scheme(1).

The primary mechanism behind the functioning of CBHI is risk pooling. Contributions are accumulated and managed to spread the risk of payment for health care among all scheme members, this makes the scheme vulnerable to adverse selection, where those with high-risk conditions make up the majority of the enrollees and those with low-risk conditions end up not participating at all (7,8). The consequences of high costs of health care, coupled with paying out-of-pocket bills include the need to sell assets or borrow money, or even resort to begging and stealing to pay for the hospital bills (6). Research done in the past has shown that insufficient community involvement and lack of trust in the scheme and its management have led to low enrolment into the community-based health insurance scheme(6,9).

Community-based health insurance, when done right, has been seen to improve the utilization of healthcare by the members of the community(10). The ability to ascertain how aware people are of the programme will help in the sustainability of the programme because being aware of what CBHI is the first step in encouraging people to enroll in the scheme. Utilization of the programme depends on a variety of factors which, as much as possible, will be explored during the course of this study.

2. Materials and Methods

A descriptive cross-sectional study was used. A multistage probability sampling technique was applied to select participants for the study. Using the Cochrane formula(11), we determined the sample size (250), with a reference prevalence of 82.5%, gotten from a descriptive cross-sectional study done to assess the awareness and willingness to participate in community health insurance scheme among household heads in Rivers State(12).

Semi-structured interviewer-administered questionnaires were designed and used to obtain information from the 250 respondents on the awareness and utilization of community-based health insurance schemes in Rumuokwurusi, Obio/Akpor LGA. The questionnaires were divided into 4 sections; Section A was for sociodemographic data of respondents, Section B contained questions assessing awareness of Community-based Health Insurance schemes, Section C was to assess utilization, and Section D was to assess the factors affecting utilization and non-utilization. Data were collected with questionnaires inputted into a Google Form.The Excel spreadsheet was retrieved and exported into IBM SPSS and analyzed. The results were presented in frequency tables. The Chi-square was done to determine the association between the outcome and independent variables with the p-value set at <0.05.

Face validity and content validity were assured by content experts (supervisors) before the questionnaires were ready to be deployed for use.

Also, data quality control measures were carried out before leaving the site of data collection; all the answered questionnaires were cross-checked by the members of the research group to ensure that they were all completely and correctly answered.

Ethical Approval was also obtained from the Rivers State Health Research Ethics Committee (RSHMB/RSHREC/2023/032), the Rivers State Primary Healthcare Management Board, and the Obio/Akpor Local Government Area Council.

Informed consent was obtained from participants, with the aims and objectives clearly explained and confidentiality of the obtained information, assured to them.

Every participant was made to understand that partaking in the study is on voluntary basis and participants were free to withdraw at any time of the study.

3. Results

3.1. Response Rate/Data Compliance

Two hundred and fifty (250) eligible respondents were given printed questionnaires, which were interviewer-administered. Of this number, all two hundred and fifty (250) respondents adequately filled and submitted the questionnaires, giving a response rate of 100%.

3.2. Sociodemographic data of respondents

Table 1. Sociodemographic characteristics of respondents

Variables	Frequency (n=250)	Percent (%)
Age		
18-25	32	12.8
26-35	91	36.4
36-45	77	30.8
46-55	25	10
56-65	14	5.6
66-75	7	2.8
76-85	3	1.2
86-95	1	0.4
Median age = 36 years		
Sex		
Female	148	59.2
Male	102	40.8

Occupation		
Student	35	14
Civil Servant	45	18
Privately employed	48	19.2
Self employed	86	34.4
Unemployed	23	9.2
Retired	13	5.2
Marital Status		
Single	93	37.2
Married	135	54
Widowed/Widower	15	6
Divorced/Separated	4	1.6
Others	3	1.2
Educational level completed		
Non-literate/Incomplete Primary	1	0.4
Primary level	7	2.8
Secondary level	66	26.4
Tertiary level	132	52.8
Post graduate level	44	17.6
Religion		
Christianity	246	98.4
Islam	3	1.2
African Traditional Religion	1	0.4
Others	-	-

Table 1 shows that of the 250 respondents, 91 (36.4%) were between the ages of 26 and 35, 148 (59.2%) were female, 86 (34.4%) were self-employed, 135 (54%) of them were married, 132 (52.8%) had completed the tertiary level of education, 246 (98.4%) were Christians. The median age of the respondents was 36 years.

Table 2. Awareness of Community-based Health Insurance Schemes

Variables	Frequency (n=250)	Percent (%)
Heard about CBHI scheme?		
Yes	114	45.6
No	136	54.4

Table 2 shows that out of 250 respondents, only 114 (45.6%) had ever heard of Community-based health insurance schemes.

Table 3: Awareness of Community-based Health Insurance Schemes present in Obio/Akpor LGA

Variables	Frequency (n=250)	Percent (%)
Aware of CBHI schemes in Obio/Akpor		
Yes	86	34.4
No	164	65.6

Table 3 shows that out of the 250 respondents, only 86 (34.4%) were aware of the existence of Community-based health insurance schemes in Obio/Akpor LGA.

Table 4: Utilization of community-based health insurance schemes

Variables	Frequency (n=250)	Percent (%)
Registration under CBHI scheme		
Yes	26	10.4
No	224	89.6

Table 4 shows that out of the 250 respondents tested, only 26 (10.4%) utilize Community-based Health Insurance Schemes.

Table 5: Factors that contributed to utilization of the Community-based Health Insurance Schemes in Obio/Akpor LGA

Variables	Frequency (n=26)	Percent (%)
Why do you utilize the scheme?*		
I am aware of CBHI and its benefits	22	84.6
The health facility is close to my house	9	34.6
It costs less, compared to paying out of pocket	8	30.8
The quality of healthcare provided is good	11	42.3
I fall sick frequently	2	7.7

I have confidence in the scheme	3	1.5

**multiple choice*

Table 5 shows that out of the 26 respondents that utilize the Community-based Health Insurance Scheme in Obio/Akpor LGA, 22 (84.6%) do so because they are aware of the scheme and its benefits.

Table 6: Factors leading to non-utilization of Community-based Health Insurance Scheme

Variables	Frequency (n=224)	Percent (%)
Why do you not utilize the scheme?*		
I am just hearing about it for the first time	134	59.8
I do not know much about the scheme	81	36.2
I do not believe that I will be treated without payment when I am sick	8	3.6
Lack of regular income to pay/renew premium	6	2.7
I do not fall sick frequently	17	7.6
There is no need, I am already old	3	1.3

**multiple choice*

Table 4.5b shows that out of the 224 respondents that do not utilize Community-based Health Insurance Schemes in Obio/Akpor LGA, 134 (59.8%) of them do not do so because they were just hearing about the scheme for the first time.

Table 7: Association between awareness, sociodemographic factors and utilization of Community-based Health Insurance Schemes

	Utilization Of CBHI Obio/Akpor LGA					
Variables	**Yes**	**Percent (%)**	**No**	**Percent (%)**	**χ2**	**P value***
Awareness						
Yes	26	10.4	60	24	55.336	0.000
No	0	0	164	65.6		
Age						
18-25	2	0.8	30	12		
26-35	6	2.4	85	34		
36-45	6	2.4	71	28.4		

46-55	7	2.8	18	7.2	15.65	0.03
56-65	3	1.2	11	4.4		
66-75	2	0.8	5	2		
76-85	0	0	3	1.2		
86-95	0	0	1	0.4		
Occupation						
Student	1	0.4	34	13.6		
Civil Servant	5	2	40	16		
Privately employed	3	1.2	45	18	10.906	0.05
Self employed	12	4.8	74	29.6		
Unemployed	1	0.4	22	8.8		
Retired	4	1.6	9	3.6		
Marital Status						
Single	3	1.2	90	36		
Married	18	7.2	117	46.8		
Widowed/Widower	5	2	10	4	15.661	0.004
Divorced/Separated	0	0	4	1.6		
Dating	0	0	3	1.2		
Living children						
Yes	22	8.8	123	49.2	8.438	0.004
No	4	1.6	101	40.4		

$p \leq 0.05$ significance level

Table 7 shows that there is a significant relationship between awareness and utilization ($\chi 2 = 55.336$, $p=0.000$), age and utilization ($\chi 2 = 15.65$, $p=0.03$), occupation and utilization ($\chi 2 = 10.906$, $p=0.05$), marital status and utilization ($\chi 2^2 = 15.661$, $p=0.004$), and living children and utilization ($\chi 2 = 8.438$, $p=0.004$).

4. Discussion

From the research done, it was seen that the awareness of community-based health insurance, despite its numerous benefits, is quite low among the residents of Rumuokwurusi, similar to a study that was done among household heads in Rivers State, which showed an awareness level of 38%(12). It also showcased the low level of awareness of community-based health insurance, emphasizing that not even up to half of the sample size were aware of the

term. A similar study done among orthopedic patients in Murtala Muhammed Specialist Hospital, Kano revealed an awareness rate of 37.8%(13). This also corresponds with a study done on households in the Nigerian capital city which revealed that 87% of the respondents were not aware of the term community-based health insurance(14).

The level of utilization of community-based health insurance by the respondents was also seen to be very low, showing that only about one in ten persons were registered under the scheme. A similar study done among households in the Nigerian capital city revealed that only 6.7% of respondents were currently under some form of insurance(14).

On assessing the factors that contributed to the utilization of community-based health insurance schemes among respondents; the study revealed that the majority of people utilize the scheme because they are aware of the scheme and its benefits. As stated earlier, the first step to encouraging people to register under the scheme is letting them know what the scheme is first and its benefits as well, as seen in a literal survey using PubMed and EconLit identified and reviewed studies that report factors affecting implementation of CBHI in sub-Saharan Africa with a focus in Nigeria(6). high enrollment was linked chiefly to increased awareness of the scheme. Over half of the respondents who utilize the scheme do so because they feel the quality of healthcare provided is good. They might have heard from other enrollees under the scheme about the quality of health care or tried it for themselves for a while and decided to continue utilizing the scheme. If the quality of care was perceived to be poor it would contribute to the low utilization of the scheme as observed in Mecha district, Northwest Ethiopia.(15) Less than half of the respondents utilize the scheme because the health facility is close to their house, this is a key factor because a far place of residence from the health facility is one of the factors that contributes to poor health-seeking behaviour. It is therefore imperative that more primary health centers be able to render these services adequately to cater to the needs of more members of the community. Some of the respondents utilize the scheme because it costs less, compared to paying out of pocket which is one of the primary purposes of developing the scheme.

The factors leading to the non-utilization of the scheme are chiefly lack of awareness and poor knowledge of the scheme, which further accentuates the need for the generation of more awareness through whatever means possible. The other notable responses were: some people felt they do not fall sick frequently, another group of people do not believe in getting treated without payment when they are sick, other respondents felt there was no need for treatment because they were too old while some did not have a stable source of income to be able to pay for the scheme. These findings further highlight the vulnerabilities of the scheme as people with low-risk conditions end up not participating leading to flooding of the scheme with only members having high-risk conditions, thereby, putting a strain on the pooled resources of the scheme(7,8).

In association with the awareness of CBHIs by the respondents and utilization of the scheme by respondents, it shows that there is a significant relationship between awareness and utilization ($\chi 2 = 55.336$, $p=0.000$). Association of sociodemographic factors and utilization among respondents who are aware of community-based health insurance revealed that there is a significant relationship between age and utilization ($\chi 2 = 15.65$, $p=0.03$), occupation and utilization ($\chi 2 = 10.906$, $p=0.05$), marital status and utilization ($\chi 2=15.661$, $p=0.004$) and living children and utilization ($\chi 2=8.438$, $p=0.004$).

5. Conclusions

Awareness of CBHI in Obio/Akpor LGA, Rivers State, is low, and even lower is utilisation amongst persons who are aware of the scheme. A statistically significant association was found between awareness and utilisation of CBHI, of which age, occupation, marital status and number of living children were important variables influencing this significance.

This implies limited financial protection as the majority of individuals may remain vulnerable to high out-of-pocket healthcare expenses. Financial barriers when accessing essential healthcare services may lead to adverse health outcomes and increased poverty levels. The low awareness and utilization of CBHI in Obio/Akpor LGA represent significant challenges

to achieving UHC goals in the region and highlight the need for Rivers State and stakeholders to develop and implement targeted interventions to expand coverage and improve access to healthcare services.

Institutional Review Board Statement: Approval of the study was obtained from the Research Ethics Committee, of the Faculty of Clinical Sciences, Pamo University of Medical Sciences, Rivers State, before proceeding with the study.

Ethical Approval was also obtained from the Rivers State Health Research Ethics Committee (RSHMB/RSHREC/2023/032), the Rivers State Primary Health Care Management Board, as well as the Obio/Akpor Local Government Area Council.

Informed Consent Statement: Informed consent was obtained from participants, with the aims and objectives clearly explained and confidentiality of the obtained information, assured to them.

Every participant was made to understand that partaking in the study is on voluntary basis and participants were free to withdraw at any time of the study.

Conflicts of Interest: Authors declare no conflict of interest.

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