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Table of Contents

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Pharmacodynamic Study of Parallel Groups Comparing the Effect of Rivaroxaban 20 Mg (Laboratorios Leti, S.A.V.) vs Rivaroxaban 20 Mg (Bayer Laboratories) on Prothrombin Time

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Abstract

Background: The prevalence of both atrial fibrillation (FA) and diabetes mellitus (DM) is increasing and they often occur together and constitute a high risk of thrombosis. Rivaroxaban is a Factor Xa inhibitor with a rapid onset and disappearance of action after oral administration; it acts by inhibiting the active form of the coagulation factor. In order to reflect the effect of the action of Rivaroxaban, we used the prothrombin time (PT); however, it´s not the most accurate, but it is the one available in our community. **Methods:** This was a prospective, randomized, analyst-blinded, parallel group clinical study to verify the efficacy of Rivaroxaban Leti 20 mg (RL) (12 volunteers vs Rivaroxaban Bayer 20 mg (RB) (13 volunteers). The variables were determination of PT and Partial Thromboplastin Time (aPTT) at baseline and at 24, 48 and 72 hours after administering a daily dose of 20 mg for three days. The determination was carried out with the IDG method (Integrated Diagnostics Group Sanzay Corporation) with an International Sensitivity Index (ISI) of 1.17 PT and aPTT were taken before the first dose, and then, every day during the next 3 days, three hours after the ingestion of their daily dose at 7 am. **Results:** The 25 healthy volunteers were similar in age, BMI, and SBP/DBP level with a greater number of men in the Bayer group. The efficacy of rivaroxaban was similar in both groups with prolongation of PTT to the 2nd day of treatment with PT, and percentage changes from baseline (14.46 ± 0.97 for RB vs 14.17 ± 0.94 RL p: 0.45), PTT results and percentage changes from the base (RB: 34 ± 4.53 RL: 33.46 ± 2.82). The safety of rivaroxaban was good in both groups with no serious adverse events. The equivalence in the logarithmically transformed PT result (ln) on day two, Mean and CI (90%) 99.2 (94.4 - 104) and 100 (99.5 - 100.8); neither the means nor the 90% confidence in-

tervals of the PT variable transformed logarithmically to ensure its normality, were far from the 80% - 125% allowed for declaration of similarity. **Conclusion:** The test formulation Rivaroxaban Asarap® 20 mg, manufactured by Leti Laboratories, is interchangeable or bioequivalent in clinical and laboratory response to the reference formulation Xarelto® manufactured by Bayer Laboratories.

Keywords

Pharmacodynamic Study, Rivaroxaban, Clinical Trial, PT, aPTT

1. Introduction

Coagulation is the result of a coordinated interaction of blood proteins, circulating cells, vasculature cells, and extracellular matrix proteins in the vessel wall This complex mechanism makes its evaluation difficult in the laboratory, which is only limited to measuring circulating coagulation proteins and circulating cells, while vascular elements are not measurable.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the tests generally used as screening to evaluate most coagulation factors. The PTTa evaluates the factors involved in the intrinsic coagulation pathway while the PT evaluates the extrinsic pathway; both agree on the factors of the common path.

To perform the PT and aPTT test, both require blood anticoagulated with sodium citrate, which works as a calcium chelator. It is very important to take into account that, if the amount of anticoagulant is inappropriate or the time elapsed between blood collection and testing is more than 4 hours, some labile factors such as factors V and VII are inactivated [1].

Prothrombin time activates coagulation when tissue factor or thromboplastin and calcium are added; the normal result ranges from 10 to 14 seconds with >60% activity. Depending on the type of thromboplastin added, the result can vary widely, which is why a standardized method has been developed to express these variations: international normalized ratio (INR).

For the aPTT test, phospholipids, calcium and a contact factor initiator such as kaolin or silica are added to the citrated plasma. The normal result ranges from 25 to 45 seconds; however, it is important to know the reference values of each laboratory [1].

Rivaroxaban (bay 59-7939) is an oral anticoagulant developed and marketed by Bayer, which acts by inhibiting the active form of coagulation factor X (factor Xa).

One way to reflect the effect of Rivaroxaban concentration is the prothrombin time, but important differences in responsiveness have been observed between thromboplastins.

Based on this, the international sensitivity index (ISI) was created, which reflects the responsiveness of each thromboplastin reagent for the reduction of vi-

tamin K-dependent coagulation factors. The recombinant tissue factor is assigned an ISI of 1.0. It is important to remember that the ISI reflects sensitivity to the effect of warfarin on PT and may not reflect the activities of factors influenced by other drugs or medical conditions [1] [2] [3].

It was debated whether the ISI established for monitoring anticoagulation with warfarin was valid for Rivaroxaban, or other Xa inhibitors, because the drug-induced effect has been shown to increase the variability between thromboplastins.

However, a study was carried out to normalize the results, with different thromboplastin reagents, which could pave the way to the establishment of universal therapeutic intervals for Rivaroxaban with selected patients.

The results of this study are consistent with the hypothesis that the ISI/INR calibration model, once used for vKa and then applied to liver disease and disseminated intravascular coagulation, is also feasible for Rivaroxaban and possibly other new direct inhibitors of fXA [3].

It is recommended to use thromboplastins whose ISI is not higher than 1.4 [4] [5].

In this study the laboratory used a reagent with an ISI of 1.17, which given the conditions of the country, was the lowest index available.

The oral bioavailability of Rivaroxaban is 80% - 100% for the 10 mg dose, regardless of food intake. Under fasting conditions, Rivaroxaban 10 mg, 15 mg and 20 mg show dose-proportional bioavailability. In a fasted state, the pharmacokinetics of Rivaroxaban is approximately linear up to approximately 15 mg once daily, and bioavailability is reduced to 66% after a 20 mg tablet; at higher doses, bioavailability decreases as a result of solubility. Food does not affect the area under the concentration-time curve or the maximum plasma concentration (Cmax) of the 10 mg dose. When the oral dose of Rivaroxaban is administered, it is absorbed rapidly, with Cmax occurring 2 - 4 hours after ingestion of the tablets [6]-[13].

At total daily oral doses of Rivaroxaban of 5 - 60 mg, Cmax ranges (mean values) from 40 μg/l to 400 μg/l and the minimum plasma concentration (Ctrough) (mean values) is 8 μg/l to 160 μg/l [10].

No relevant accumulation occurs beyond steady state in healthy individuals [6]. The elimination of Rivaroxaban from plasma occurs with a terminal half-life of 5 - 9 hours in young individuals [8] [12] and 11 - 13 hours in the elderly [14]. Rivaroxaban has a dual mode of elimination [15].

Of the administered dose, approximately two-thirds undergo metabolic degradation, half of which is eliminated through the kidneys and the other half via the hepatobiliary route. The last third of the administered dose undergoes direct renal excretion [16] [17].

In our country, we need to demonstrate the similarity between second brands of an active ingredient, comparing them with the innovative product, in our case the rivaroxaban from Leti Laboratories, was compared with rivaroxaban from

Bayer Laboratories, Xarelto.

2. Objective

To verify, under a parallel design, the pharmacodynamic equivalence of Rivaroxaban from Leti Laboratories: (RL) 20 mg tablets in three days, one dose/day, test product, compared to the Rivaroxaban product from Bayer Laboratories, reference product, Xarelto® (RB) of 20 mg in three doses, one dose/day, in a population of healthy volunteers.

3. Materials and Methods

This was a randomized, analyst-blinded, parallel-group clinical study, and was carried out at the Uslar Medical Center in Venezuela during 2023.

We included healthy volunteers, aged between 18 to 45 years; their good health was confirmed by complete medical examination (clinical history, physical examination, personal history) and paraclinical tests (laboratory routine: complete hematology, urea, creatinine, glycemia, cholesterol, triglycerides, PT, aPTT, liver biochemistry, HIV by the Elisa method, serology for hepatitis B and C, urine and feces, ECG and chest x-ray).

People were summoned by public notice. Those who attended the notice received a pre-selection form, and an information form about the study. If they were interested in participating in it, they received the subjects' informed consent and once signed, the volunteer entered the study.

We excluded from the study subjects with the following findings:

Quetelet index less than 18 or greater than 30. Volunteers with a history of nephropathies, liver diseases (including viral processes), hematological disorders, gastritis, gastric ulcer, rectocolitis, allergy to similar medications, coagulation disorders, cardiovascular diseases, central nervous system (CNS), metabolic diseases or any condition that may interfere with the absorption, metabolism and/or excretion of the drug. Active infections, whether viral, bacterial of any type, or fungal. Subjects under any therapeutic regimen or who have been under any therapeutic regimen during the 30 days prior to the study, including oral contraceptives (depending on the medication used, the period may be reduced to 15 days), always subject to the discretion of the study coordinating doctor.

Subjects with a history of alcohol abuse, drug abuse, smoker of more than 10 cigarettes a day. Blood donor in the last 3 months. Subjects who participated in a similar study in the last 3 months. Allergy to the study drug. Pregnancy (positive pregnancy test) and/or breastfeeding period. Obvious mental illnesses or behavioral disorders that may interfere with research.

At the beginning, the volunteers underwent interrogation and clinical examination in order to guarantee their status as healthy volunteers. On the first day, 6 cc of blood were drawn to determine baseline PT and aPTT. This determination was performed with the IDG Integrated Diagnostics Group Sanzay Corporation method, with an ISI of 1.17 with the the coagulometric method.

Subjects were randomly assigned to one of two groups: Rivaroxaban Leti (RL) 20 mg vs Rivaroxaban 20 mg from Bayer Laboratories (RB).

Each subject was given a box with four tablets of the study product that he should take that day and for the next two days (1 window tablet).

Drug under study, chemical name: 5-cloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3 oxazolidin-5 il}metil)-2-tiofeno-carboxamida; Generic name: Rivaroxaban; tradename Asarap®, pharmaceutical form tablets, manufacturer laboratory, Leti Laboratories, S.A.V. Venezuela, dose 20 mg.

On the first day and the following two days, the subject had to take the tablet at 7 am and undergo the PT and aPTT test, for which 6 cc of blood was withdrawn for the determination, 3 hours after taking the tablet, or be at 10 am.

The size of the sample was calculated taking into consideration the PT data obtained from the results of a healthy population in a previous study: Standardization of quality control in the haemostasis laboratory Olga Silvia Pantaleón Bernal, María Eugenia Triana Mantilla, Cs Milagros Tomasa García Mesa La Habana Cuba, Instituto Nacional de Angiología y Cirugía Vascular, NACV. In that study, average PT was 13.1 seconds with a standard deviation of 0.94. Using this data gives us a power greater than 90% to detect a difference of 2 points in PT with an Alpha error of 0.05, with 12 subjects in each group.

The variables: age, height, BMI, SBP, DBP, and pulse were evaluated using Student's t-test, paired within group and unpaired between groups. The variable sex was evaluated using Chi^2.

The variables: PT and PTT were evaluated using the Wilcoxon Rank Test within group and Mann Whitney U between groups.

4. Results

Thirty-nine volunteer subjects applied, of which 14 were removed due to alterations in laboratory examinations. They were referred to different specialists to address these alterations.

There were no differences between the groups in relation to age, sex, weight, body mass index, blood pressure or pulse, these variables remained unchanged during the study and at the final examination, 15 days after the end of the study.

There were no differences between the anthropometrical variables and the background between both groups (Table 1).

In both groups, there was a prolongation of prothrombin time (PT). When the comparative analysis of the data transformed into logarithms in base e, was carried out to ensure their normality, we did not find any differences between the groups in the prolongation of PT (Table 2).

In both groups, there was a prolongation of activated partial thromboplastin time (aPTT). When the comparative analysis of the data transformed into logarithms in base e, was carried out to ensure their normality, we did not find any differences between the groups in the prolongation of aPTT (Table 3).

When we carried out the relationships of the PT logarithmically transformed

Table 1. Description of the evaluated population.

Parameter	Rivaroxaban Bayer	Rivaroxaban Leti	p
Age	31.8 ± 9.3	32.0 ± 9.6	0.95
M/F Sex	11/2	6/6	0.58
Weight	71.2 ± 13.3	75.3 ± 13.3	0.46
Size	1.69 ± 0.1	1.72 ± 0.1	0.51
BMI	24.83 ± 3.9	25.6 ± 4.7	0.66
PAS	113.9 ± 10.4	115.4 ± 9.2	0.69
PAD	69.2 ± 6.7	67.8 ± 6.6	0.58
Pulse	66.0 ± 9.6	70.4 ± 7.6	0.21
Family history	Arterial Hypertension N = 4 Diabetes N = 2 Osteoporosis = 1 Alcoholic Liver Cirrhosis = 1	Arterial Hypertension N = 4 Diabetes N = 1. Renal Lithiasis N = 1 Thalassemia N = 1 Prostate Cancer N = 1. Breast Cancer N = 1	

Table 2. PT results, and percentage changes in the base.

	Rivaroxaban Bayer					Rivaroxaban Leti			
n°	Start	Day 1	Day 2	Day 3	N°	Start	Day 1	Day 2	Day 3
1	13	13	16	15	2	14	14	15	15
4	13	15	13	14	3	14	14	15	16
6	14	14	14	15	5	14	14	15	15
8	12	13	15	16	7	13	14	14	15
10	14	14	14	14	9	14	14	15	15
12	13	14	14	14	13	15	14	15	14
14	14	14	15	15	16	13	13	13	14
15	15	16	16	16	18	14	14	14	14
17	14	13	14	13	20	14	15	14	13
19	15	13	15	14	22	13	14	12	12
21	14	13	14	13	23	14	14	14	14
24	14	13	13	13	25	15	15	14	14
26	14	16	15	13					
Average	13.77	13.92	14.46	14.23		13.92	14.08	14.17	14.25
SD	0.83	1.12	0.97	1.09		0.67	0.51	0.94	1.06
	p between groups					063	065	045	096
% Change from base		1.12	5.03	3.35			1.20	1.80	2.40

Table 3. aPTT results and percentage changes in the base.

Rivaroxaban Bayer					Rivaroxaban Leti				
N°	Start	Day 1	Day 2	Day 3	N°	Start	Day 1	Day 2	Day 3
1	30	34	28	32	2	31	28	32	34
4	34	32	37	38	3	28	34	37	32
6	34	38	37	39	5	36	35	35	34
8	34	31	36	40	7	34	34	37	35
10	40	34	31	31	9	32	35	36	34
12	32	32	34	31	13	32	41	38	38
14	30	32	32	32	16	28	28	28	25
15	36	40	35	38	18	40	41	36	42
17	34	39	31	34	20	31	31	29	28
19	42	34	36	37	22	32	30	27	28
21	34	39	32	35	23	39	32	36	44
24	26	31	31	32	25	36	39	34	35
26	27	34	35	31					
average	33.31	34.62	33,46	34,62		33.25	34.00	33.75	34.08
SD	4.53	3.25	2.82	3.38		3.86	4.53	3.82	5.55
p between groups						**0.97**	**0.70**	**0.83**	**0.77**
% Change from base		3.93	0.46	3.93			2.26	1.50	2.50

Table 4. Equivalence in the result of logarithmically transformed PT (Ln).

	Start	Day 1	Day 2	Day 3
Average %	100.4	100.5	99.2	100.1
Minimum %	95.5	95.6	94.4	95.1
Maximum %	105.4	105.4	104.1	105.0

Table 5. Equivalence in the logarithmically transformed aPTT Result (Ln).

	Start	Day 1	Day 2	Day 3
Average %	100.0	99.4	100.2	99.3
Minimum %	99.4	98.7	99.5	98.5
Maximum %	100.6	100.1	100.8	100.2

means, as well as the 90% confidence intervals, we found that neither the means, nor the minimum and maximum values, were outside the 80% - 125% range required for Declaration of Similarity, at any time (Table 4).

When we carried out the relationships of the aPTT logarithmically trans-

formed means, as well as the 90% confidence intervals, we found that neither the means, nor the minimum and maximum values, were outside the 80% - 125% range required for Declaration of Similarity, at any time (**Table 5**).

5. Discussion

In the Factor CKET-AF study, Rivaroxaban was not inferior to warfarin for the prevention of stroke and systemic embolism [2] in the "intention to treat" analysis, while in the "per protocol" analysis it achieved statistical superiority with a reduction in 21% rate of stroke or embolism versus warfarin.

Rivaroxaban is a potent and selective inhibitor of factor Xa. It is absorbed orally and its bioavailability is greater than 80%. Its effect is to prolong the prothrombin time and the activated partial thromboplastin time. Its pharmacodynamic equivalence was carried out to compare action on prothrombin time in healthy volunteers [3] based on changes in laboratory parameters, PT and PTT in healthy volunteers.

The Bioequivalence studies carried out in healthy volunteers with a dose of 10 mg y 20 mg, in a 4-period, randomized, open-label and crossover study in healthy subjects under fasting or fed conditions, indicated that the 2 different formulations of rivaroxaban compared were bioequivalent [18] [19].

On this occasion, it has been decided to compare two formulations of rivaroxaban evaluating its action on the coagulation parameters. The two groups of volunteers were similar at the beginning of the study in terms of age, sex, weight, height, SBP, DBP, pulse and history (**Table 1**).

In both groups, there was a prolongation of PT and aPTT, without reaching a difference between groups and their response (**Table 2** and **Table 3**).

When the relationship between the PT and aPTT, logo-transformed variables, were analyzed, it was found that neither the means nor the confidence intervals of both variables are far from the 80% to 125% interval. The test formulation Rivaroxaban Leti 20 mg, manufactured by Leti Laboratories (Asarap®) is interchangeable or equivalent in clinical and laboratory response to the reference formulation Xarelto®, manufactured by Bayer (**Table 4** and **Table 5**).

A bioequivalence study was carried out with this same product Rivaroxaban from Laboratorios Leti, to demonstrate the bioequivalence (BE) and safety of a generic formulation of rivaroxaban by comparing their pharmacokinetic (PK) parameters through statistical data and criteria of validation. Oral tablet formulations of 20 mg of a commercial product rivaroxaban reference (R) were tested against a generic of Leti Laboratories product test (T) in 24 healthy adults under fasting condition. The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, and crossover study. Blood samples were collected pre-dose and at specified intervals up to 48-h post-dose to evaluate PK parameters by quantifying the concentration of rivaroxaban in plasma using a validated Liquid chromatography-mass spectrometry (LC-MS/MS) method of analysis. Statistics and confidence intervals (CIs) were

calculated for BE purposes. Results: The geometric means of the T/R ratios and 90% confidence intervals (CIs) were: Cmax 87.80% (82.74% - 93.12%), AUC0-t 85.96% (81.88% - 90.24%), and AUC0-∞ 86.13% (82.2% - 90.35%). All PK parameters are within BE acceptance range of 80% - 125% for demonstration of average bioequivalence [20].

According to these studies, rivaroxaban, from Leti Laboratories in Venezuela, has been shown by biequivalence and pharmacodynamic equivalence, to be similar to the international reference product.

6. Study Limitations

The absolute bioavailability of rivaroxaban, at higher doses, rivaroxaban shows decreased absorption, with a dose-dependent reduction in bioavailability and absorption rate. This effect is more marked on an empty stomach than after eating, when using the 20 mg presentation we could have reductions in the bioavailability of rivaroxaban that could affect the PT and PTTa results.

On the other hand, although it is recommended that a reagent be used to determine PT with an ISI value of less than 1.4, ideally it should be closer to 1.0. In this study, a reagent with an ISI of 1.17 was used, which gave the conditions of the country, was the lowest index available.

Conflicts of Interest

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

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A Meta-Analysis of the Prognostic and Clinicopathological Significance of circZFR in Human Gastrointestinal Cancers

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Abstract

Background: Studies of gastrointestinal (GIT) cancers have shown that circZFR could be involved in the development and progression of various GIT cancers. However, small sample sizes limit the clinical significance of these studies. Here, a meta-analysis was conducted to ascertain the actual involvement of circZFR in the development and prognosis of GIT cancers. **Methods:** PubMed, Embase, Web of Science, and the Cochrane Library were searched up to December 31, 2023. Hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were pooled to evaluate the association between circZFR expression and overall survival (OS). Publication bias was measured using the funnel plot and Egger's test. **Results:** 10 studies having 659 participants were enrolled for meta-analysis. High circZFR expression was associated with poor OS (HR = 1.4, 95% CI: 1.20, 1.70). High circZFR expression also predicted larger tumor size (OR = 4.38, 95% CI 2.65, 7.25), advanced clinical stage (OR = 5.33, 95% CI 3.10, 9.16), and tendency for distant metastasis (OR = 2.89, 95% CI: 1.62, 5.11), but was not related to age, gender, and histological grade. **Conclusions:** In summary, high circZFR expression was associated with poor OS, larger tumor size, advanced stage cancer and tendency for distant metastasis. These findings suggested that circZFR could be a prognostic marker for GIT cancers.

Keywords

CircZFR, Gastrointestinal, Prognostic, Significance, Meta-Analysis

1. Background

In humans, approximately 93% of the genome can be transcribed into RNA yet less than 2% are capable of being translated into proteins. The rest are termed non-coding RNAs [1]. Among these are circular RNAs (circRNAs) [2] [3] characterized by highly conserved closed loop structures that lack a free 5 cap and 3' tail, making them resistant to degradation by exonucleases. While most circRNAs are derived from exons and found in the cell cytoplasm, their mechanism of formation remains largely unknown [4].

CircRNAs primarily carry out their biological activities by acting as competing endogenous RNAs (ceRNAs), helping to sponge miRNAs, control transcription, and translation and carry out other epigenetic tasks. For instance, upregulation of circCDR1as in gastric cancer suppresses miR-7 activity which leads to more aggressive oncogenic phenotype mediated by PTEN/PI3K/AKT pathway [5]. Various studies have demonstrated their ability to regulate aging [6], diabetes [7], and various tumors [8] [9] [10]. In tumors, the involvement of circRNAs has been demonstrated in tumor development, proliferation, and metastasis [11] [11]. Recent studies have also demonstrated their involvement in tumor resistance to chemotherapy [12] [13].

Circular RNA zinc finger RNA-binding protein (Circ-ZFR) is a transcription product of zinc finger RNA-binding protein (ZFR) gene mapped to chromosome 5p13.3. Studies of gastrointestinal (GIT) cancers have shown that it could be involved in the development and progression of various GIT cancers such as hepatocellular carcinoma (HCC) [14], gastric cancer (GC) [15], and colorectal cancer (CRC) [16] among others. While the majority of these studies have demonstrated its oncogenic property, their small sample sizes limit their clinical significance. In this study, we sought to conduct a meta-analysis of all these studies to ascertain the actual involvement of circZFR in the development and prognosis of GIT cancers.

2. Methods

Records search strategy

This meta-analysis was conducted according to the 2020 updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [17]. A comprehensive database search was conducted by two independent reviewers (CCB and ET) in PubMed, Embase, Web of Science, and the Cochrane Library up to December 31, 2023. The key items in the search strategy were: "circZFR" OR "circ_ZFR" OR "circ-ZFR" OR "circRNA ZFR" OR "circular RNA ZFR" OR "circ_0072088" OR "circ_0072083" OR "Circ_103809" OR "circRNA_103809" OR "Hsa_circRNA_103809" OR "Circular RNA hsa_circRNA_103809". Additionally, references of included articles were manually searched for relevant articles, and a general search on google and google scholar were conducted for articles missed in the database search.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were as follows: Inclusion criteria: 1) Pa-

tients definitely diagnosed with HCC by histopathology; 2) studies that focused on clinical diagnostic or prognostic value of circZFR in HCC; 3) studies where circZFR was assigned to high expression group (high) or low expression group (low) based on its relative expression level; 4) studies that provided enough information on the correlation between circZFR expression level and overall survival (HRs with 95% CIs) or clinical characteristics (age, gender, stage, grade, and so on). Studies were excluded if: 1) they were duplicate publications; 2) focused on the structures or functions of circZFR, without any clinical diagnostic or prognostic information; 3) had non-extractable data; 4) and had no original data e.g. reviews and meta-analysis.

Data extraction and study quality assessment

Included studies were independently assessed in detail by two investigators (CCB and ET) for data extraction. Each investigator extracted data independently and any discrepancies were settled by consensus. None of the studies was an RCT. The baseline data extracted from each study were: 1) first author name and year of study, country, cancer type, clinical stage, tumor size, cut-off value, follow-up time, detection method, adjuvant therapy before surgery, survival analysis method, and outcome measure method; 2) hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) of circZFR for OS or clinicopathologic parameters. For studies that did not directly present HRs, the software Engauge Digitizer (version 4.1) was used to calculate it from the Kaplan-Meier curve. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) [18].

Data synthesis and statistical analysis

The statistical analyses were conducted in Review Manager (RevMan 5.4). HRs or ORs with corresponding 95% CIs were used to describe the relationship between circZFR expression and the prognosis or clinical characteristics. The chi-squared test and I^2 statistics was used to assess the heterogeneity among studies. A value of $p < 0.05$, $I^2 > 50\%$ was considered to be study heterogeneity. Random effect model was used since the studies had varying methodologies. The funnel plot and Egger's test was used to estimate the potential publication bias. A P value of $p < 0.05$ was considered statistically significant.

3. Results

Study selection criteria

Thorough database search yielded 89 studies in total, with 49 duplicates that were promptly excluded. 3 studies were reviews and so excluded as well. The remaining 37 studies had their full-text articles extracted and thoroughly assessed. 24 of them did not have clinical analyses while 3 had unextractable data. These were all excluded leaving 10 studies [14] [15] [19]-[26] all from China for final inclusion in the meta-analysis. All the studies combined had a total of 659 participants. The selection flow chart is presented in **Figure 1**.

Description of included studies

Detailed information on the enrolled studies is presented in **Table 1**. Studies

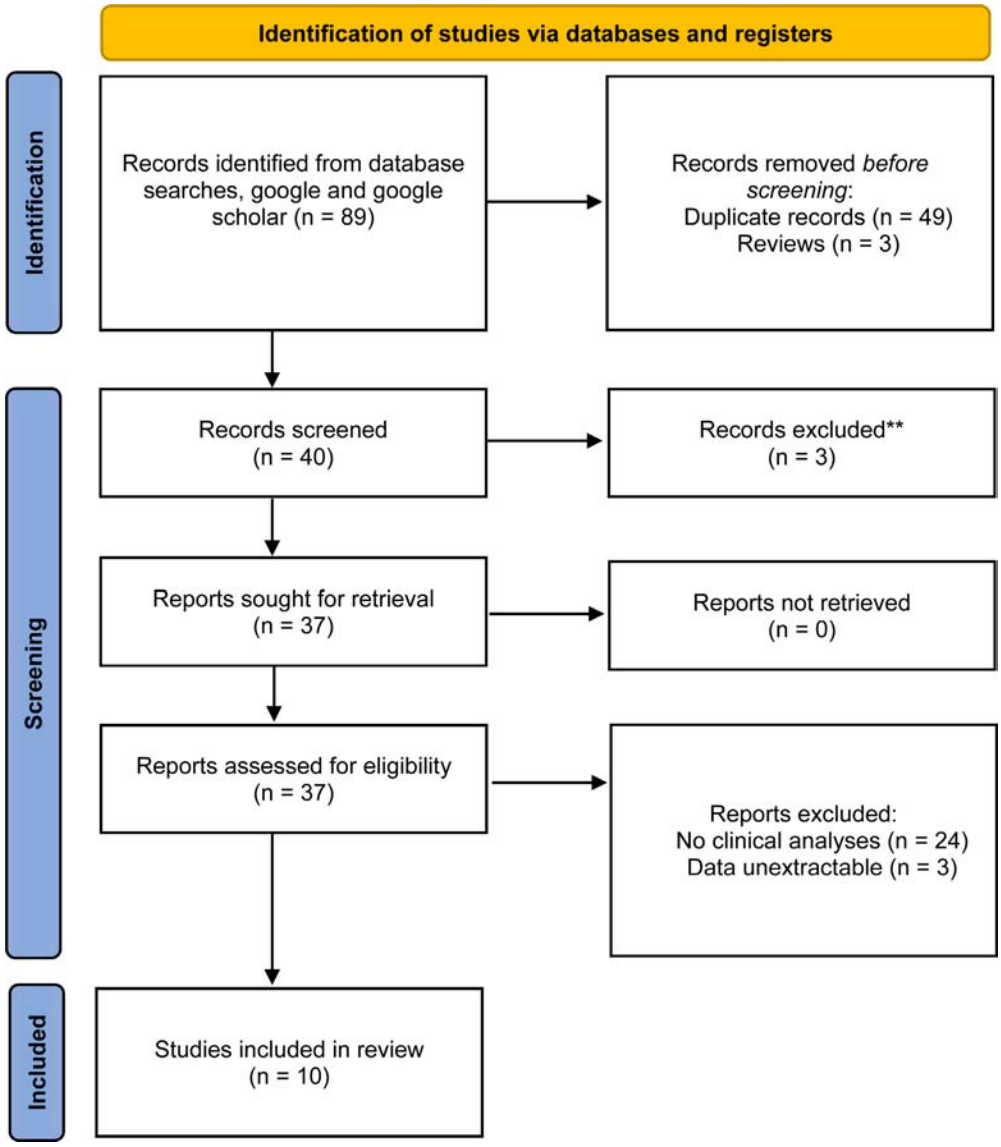

Figure 1. Flowchart of study selection criteria.

were published between 2017 to 2021, and all were conducted in China. CircZFR expression level was detected by quantitative real-time polymerase chain reaction (qRT-PCR) in all studies with the sample size ranging from 30 to 170. Analyses were both univariate and multivariate. Outcome measures were clinicopathological parameters (CP) and overall survival (OS). Only 4 studies mentioned the overall follow up time of the patients, all 60 months and more. Mean and median expression of circZFR were used as cut-off values. NOS score in all the studies was ≥ 7, indicating high overall quality of the studies.

Association between circZFR expression and OS

Four studies [15] [19] [20] [21] comprising 360 participants qualified for pooled OS analysis. The studies were generally homogeneous (I^2 = 0%, p = 0.94). The OS results indicated that high expression of circZFR was associated with relatively poor OS (HR = 1.4, 95% CI: 1.20, 1.70) (**Figure 2**).

Table 1. Summary of the main characteristics of included studies.

Author	Country	Cancer type	Clinical stage	Sample size	Cut off value	Follow up (months)	Detection method	Adjuvant therapy	Survival analysis	Outcome measure	NOS
Cedric, 2020	China	HCC	T1 - T4	62	Mean	-	qRT-PCR	None	Univariate	CP	7
Li, 2021	China	HCC	I-III	49	NA	-	qRT-PCR	None	Univariate	CP	7
Lin, 2021	China	HCC	I-IV	50	Median	60	qRT-PCR	None	Multivariate	OS, CP	9
Tan, 2019	China	HCC	-	80	Mean	60	qRT-PCR	None	Univariate	OS	8
Xu, 2021	China	HCC	I-IV	40	NA	-	qRT-PCR	None	Univariate	CP	7
Yang, 2019	China	HCC	I-IV	30	Median	-	qRT-PCR	None	Univariate	CP	7
Zhan, 2020	China	HCC	I-IV	60	NA	100	qRT-PCR	None	Univariate	OS, CP	9
Fang, 2020	China	ESCC	I-IV	58	Median	-	qRT-PCR	None	Univariate	CP	7
Huang, 2020	China	GC	-	60	NA	60	qRT-PCR	None	Univariate	OS	8
Zhang, 2017	China	CRC	I-IV	170	NA	-	qRT-PCR	None	Univariate	CP	7

Abbreviations: CRC: colorectal cancer; CP: clinicopathological parameters; ESCC: esophageal squamous; GC: gastric cancer; HCC: hepatocellular carcinoma; N/A: not available; NOS: Newcastle-Ottawa Scale; OS: overall survival; qRT-PCR: quantitative real-time polymerase chain reaction.

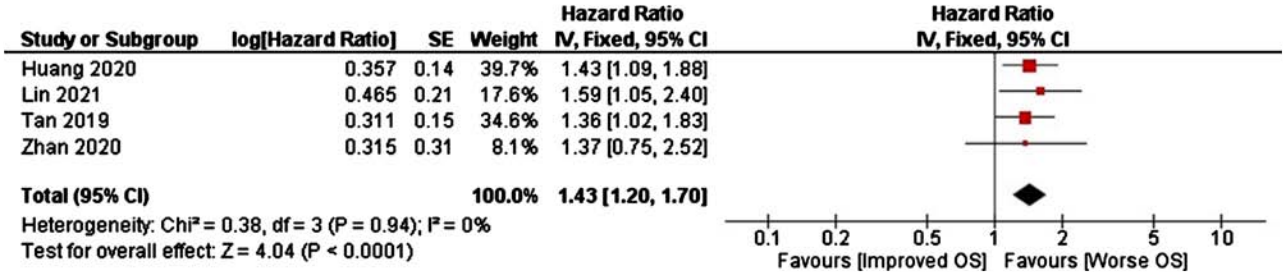

Figure 2. Forest plot evaluating the association between circZFR expression and OS.

Association between circZFR expression and clinicopathological parameters

Age, gender, tumor size, clinical stage, distant metastasis (DM), lymph node metastasis (LNM), and histology grade were the clinicopathological parameters analyzed to evaluate their correlation with circZFR expression (Table 2). Notably, six studies enrolled to explore the correlation between circZFR expression and tumor size, demonstrating that higher circZFR expression predicted larger tumor size (OR = 4.38, 95% CI 2.65, 7.25). Similarly, the upregulation of circZFR expression indicated advanced clinical stage (OR = 5.33, 95% CI 3.10, 9.16), and distant metastasis DM (OR = 2.89, 95% 1.62, 5.11) (Figure 3). Statistically insignificant association were found between circZFR expression and age (OR = 1.44, 95% CI 0.94, 2.22), gender (OR = 1.06, 95% CI 0.72, 1.57), and histological grade (OR = 1.75, 95% CI 0.52, 5.93) (Figure S1).

Publication bias analysis

The potential for publication bias was estimated using the funnel plot method and Egger's test. The results showed no significant publication bias as indicated

Table 2. Association between circZFR and other clinicopathological parameters.

Subgroup	Studies	Total participants	Odds ratio (95% CI)	P value	Model	Heterogeneity (I^2)
Age	7	479	1.44 (0.94 - 2.22)	0.09	Random	6%
Sex	8	519	1.06 (0.72 - 1.57)	0.77	Random	0%
Tumor size	6	397	4.38 (2.65 - 7.25)	0.0001	Random	0%
Clinical stage	6	397	5.33 (3.10 - 9.16)	0.00001	Random	0%
LNM stage	3	290	2.89 (1.62 - 5.11)	0.003	Random	0%
DM	2	232	2.09 (1.01 - 4.32)	0.05	Random	0%
Histology Grade	3	258	1.75 (0.52 - 5.93)	0.37	Random	73%

Abbreviations: CI: confidence interval; DM: distant metastasis; LNM: lymph node metastasis; OR: odds ratio.

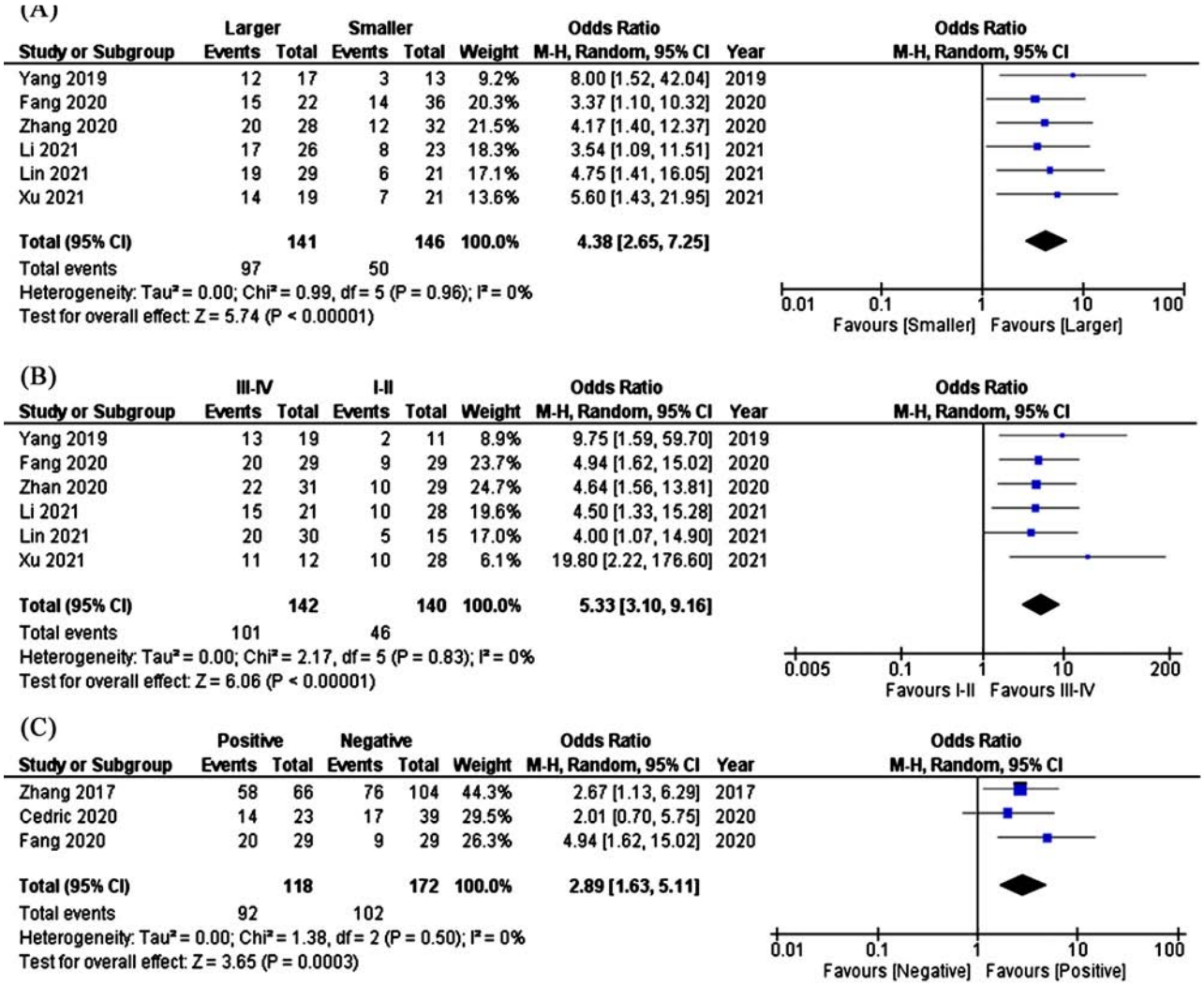

Figure 3. Forest plots evaluating the correlation between circZFR expression and clinicopathological characteristics of the patients that included; tumor size (a), clinical stage (b), and distant metastasis (c).

by the symmetrical distribution of study points in the funnel plot (**Figure S2**). Furthermore, Egger's test ($p = 0.172$) indicted no publication bias.

4. Discussion

Recent studies indicate that circRNAs possess potentials for cancer prognostic and treatment applications given their stability in body fluids such as plasma and serum, and specificity in certain cancers [27]. Circ ZFR is one of such circRNAs whose potential as a cancer driver gene has been verified in different studies. It is overexpressed in some GIT cancers [15] [20], while under expressed in others [26]. Analysis of its expression indicates strong association with certain clinicopathological characteristics in GIT cancers, making it a potential biomarker for prognostic prediction of these cancers.

In this meta-analysis, we assessed the association between CircZFR and GIT cancers. In the first step, we determined the correlation between circZFR expression and the overall survival (OS) of patients with GIT cancers. The pooled HR revealed that high circZFR expression was associated with poor OS. This was true whether the cut-off values of CircZFR expression were captured in mean or median in the original studies. Indeed, circZFR overexpression has been shown to promote cell proliferation, migration and invasion in GIT cancers such as esophageal squamous cell carcinoma [22], hepatocellular carcinoma [24] and gastric cancer [15] among others.

In relation to other major patient characteristics, we evaluated the association between circZFR expression and the patients' age, gender, tumor size, clinical stage, distant metastasis and histology grade. Our findings showed that higher circZFR expression was correlated with larger tumor size, advanced clinical stage, and distant metastasis. Statistically insignificant associations were noted in age, gender and histological grades. While circRNAs effect their biological functions by acting as miRNA molecular sponge, or regulating transcription of genes, and sometimes translation into proteins or small peptides, the function and mechanism of action of circZFR in promoting GIT cancers is still largely unclear and needs further research to unravel.

In terms of heterogeneity, the studies were largely homogenous as demonstrated by the I^2 values in the various forest plots. This is likely because all the studies were conducted in China and most had similar designs. Similarly, there was no publication bias as indicated by the symmetrical shape of the funnel plot and the result of the Egger's test. These findings improve the reliability of the meta-analysis.

This study had the following limitations that may affect interpretation. Firstly, all the included participants were from China, making generalization of results across different regions of the world difficult. Secondly, only four studies qualified for the prognosis meta-analysis, which greatly limited the wide application of the meta-analysis results. Finally, since many studies never reported HRs with their 95% CIs in the main articles, we extracted these values from the Kap-

lan-Meier curves. This could have an effect on their accuracy.

5. Conclusion

In summary, this meta-analysis demonstrated that upregulation of circ-ZFR expression is highly correlated with poor prognosis of GIT cancers. It is also correlated with certain clinicopathological parameters such as larger tumor size, advanced clinical stage, and distant metastasis among patients of Chinese origin. This demonstrates that circZFR could be a prognostic biomarker for GIT cancers. However, large-scale studies from different regions of the world will be required to verify these results.

Authors' Contributions

CCB designed the study, performed the literature retrieval, data analysis, interpretation and drafted the manuscript. ET contributed to the study methodology, performed literature retrieval and data analysis and reviewed the manuscript. ZY participated in the data analysis and assisted in creating the figures and reviewed the manuscript. JCT supervised the study. All authors read and approved the final manuscript.

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Availability of Data and Materials

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

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

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Supplementary

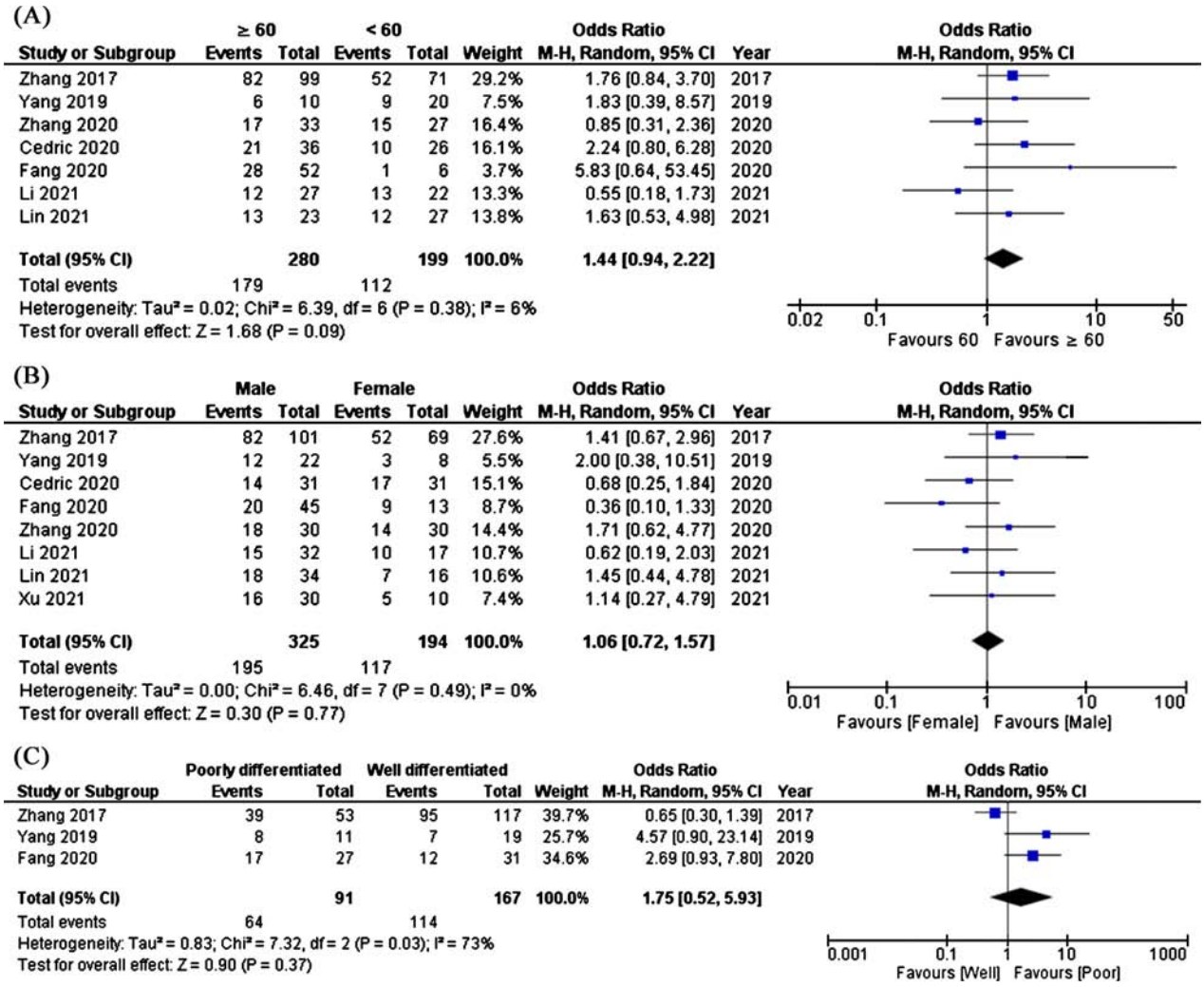

Figure S1. Forest plots of the association between circZFR expression and clinicopathological parameters, including patient age (a), gender (b), and tumor histology grade (c).

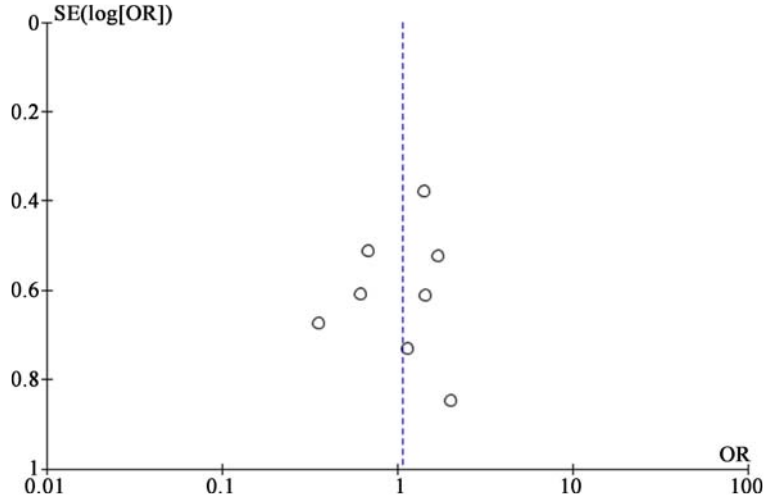

Figure S2. Funnel plot.

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Adherence to Pharmacotherapy in Post-Menopausal Women with Hypertension or Metabolic Syndrome: Real World Experience

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Abstract

Background: Adherence to medications is dependent upon a variety of factors, including individual characteristics of the patient, interactions with health care providers, and medication complexity. Even though several studies were conducted to test intervention strategies, results are uncertain. **Aim:** The aim of the study is to assess if a tailored combined intervention strategy improves medication adherence in a large population of post-menopausal women affected by hypertension or metabolic syndrome. **Methods:** We enrolled 6833 patients aged 50 to 69 years, 85.7% with hypertension, and 14.3% with metabolic syndrome. A network between patients, general practitioners, and cardiologists was established. Interventions included education, adequate information to patients, a simplified scheme of treatment, and periodic adherence assessment. These were either delivered as healthcare provider supports or using modern technology. Medication adherence was estimated by the proportion of days covered for all classes of drugs after the index date. **Results**: Non-adherent hypertensive women were 297 (5%), and those with metabolic syndrome were 73 (7.4%) ($p < 0.02$). Considering only patients with cardiomyopathy non-adherent were 234 (5.4%), while without cardiomyopathy 136 (5.3%); non-adherent hypertensive postmenopausal women with cardiomyopathy were 194 (5.2%), non-adherent postmenopausal women with metabolic syndrome and cardiomyopathy were 40 (7.2%) ($p < 0.04$). Non-adherent hypertensive postmenopausal women without cardiomyopathy were 103 (4.9%), and non-adherent postmenopausal women with metabolic syndrome and without cardiomyopathy were 33 (7.7%) ($p < 0.01$). **Conclusions:** The rate of non-adherence in both settings of postmenopausal women was 7.7%, much lower than that described in the literature. This rate

*These authors contribute equally to the work.

was increased in patients with metabolic syndrome; probably it is related to the complexity of the therapeutic scheme or to a poor consciousness of the disease. Therefore, implementing a tailored combined intervention can improve significantly patients' adherence to medical therapy.

Keywords

Adherence, Cardiovascular Prevention, Postmenopausal Women, Hypertensive, Metabolic Syndrome

1. Introduction

The risk of CVD increases markedly after menopause [1]. Menopause is characterized by a decrease in the endogenous production of estrogen, which is associated with vascular dysfunction, increased blood pressure, redistribution of body fat toward abdominal areas, and hyperlipidemia, all of which increases CVD risk [1]. The typical age range for menopausal transition is between 45 and 55 years; menopause onset at an age younger than 45 years is considered early menopause [1]. Early menopause may be more detrimental to women's cardiovascular health because of the early cessation of estrogen's cardiovascular protection [1]. Early menopause has been associated with an increased risk of coronary heart disease (CHD) [2] and heart failure (HF) and less consistently with stroke [3]. Midlife women with underlying metabolic disorders face a higher risk of CVD [2]. Although effective medications that control risk factors and reduce the risk of cardiovascular disease are available, low adherence to drugs, especially to the polypill approach, persists as major public health and clinical challenge. Interventions to promote medication adherence may target a number of identified patient specific-barriers: lack of symptoms [4], depression [5], low health literacy, medication complexity, cost, and concerns, use of alternative medicine, poor health care system perceptions; poor communication or provider-patient interaction, medication side effects; forgetfulness; inadequate social support or coping, caring for dependents, and lack of motivation for self-care [6] [7] [8]. Interventions that target these factors can be classified as informational, behavioral, social, or combined [9]. Informational interventions use didactic or interactive approaches to educate and motivate patients and to increase their understanding of their condition and its treatment [10]. Behavioral interventions move beyond the cognitive approaches of informational interventions to influence patient behaviors by shaping, reminding, or rewarding desired behaviors, whereas social interventions enlist family members or others in supporting medication adherence [10]. Finally, combined interventions include elements of more than one informational, behavioral, or social strategy. Strategies may vary in intensity, setting as an individual or group, mechanism of delivery as face-to-face or technology-mediated, and required personnel as a physician, allied health professional, or lay individual [11]. When evaluating the effectiveness of interven-

tions to improve adherence, consideration should be given to the adherence measure used. Validated objective as pharmacy fill or electronic monitoring [12] [13] [14] and subjective as self-report [15] [16] measures for assessing medication-taking behavior are available. However, notwithstanding a large number of studies previously conducted, the effectiveness of the interventions tested is controversial. In this study combined interventions to promote pharmacological adherence were tested. Pharmacy fill was used to assess medication-taking in a postmenopausal woman with a high risk of cardiovascular events.

2. Methods

2.1. Study Design

This is a retrospective observational study. Ethical approval has been obtained from institutional review boards at the study sites.

2.2. Study Population

We included in our study women in menopause, only after, at least, twelve consecutive months of amenorrhea. The mean age of the patients was 59.9 ± 12 years. None of them was on hormone replacement therapy because estrogen can interfere with arterial stiffness. 5857 of them had a diagnosis of arterial hypertension according to the 2018 European Hypertension Guidelines [17]; moreover, 976 menopausal patients were diagnosed with metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III [18] (**Table 1**). TTE was performed with the patient in left lateral decubitus, after 10 minutes of resting, with the exam table elevated by 30˚. The exam was carried out with 3.5 MHz probe, with ECG trigger. We used echo-Doppler system equipped with a multifrequency transducer, Philips, Epiq 7, Utrasound System for Cardiology, Healthcare, viale Sarca 235, Milan (Italy). We assessed: intraventricular septum thickness in diastole (IVSd) and in systole (IVSs), left ventricular diastolic end-systolic diameter (LVDD), left ventricular posterior wall thickness during in diastole (LVPWd) and in systole (LVPWs), ejection fraction (EF), fractional shortening (FS). Peak velocities of early (E wave) and late (A wave) trans-mitral flow and deceleration time (DT) were determined, E' wave and A' wave by tissue Doppler

Table 1. Main characteristics of the sample.

PMW	6833
HYPERT	5857
HCMP	3752
MeTs	976
MCMP	550

PMW: postmenopausal women enrolled. HYPERT: postmenopausal women with hypertension. HCMP: postmenopausal women with hypertensive cardiomiophaty. MeTs: postmenopausal women with metabolic syndrome. MCMP: postmenopausal women with hypertensive cardiomiophaty.

imaging were determined at mitral annulus level. E/A ratio, E'/A' ratio and E/E' ratio was calculated. LV mass (LVM) was determined according to the formula by Devereux *et al.* [19] and indexed according to body surface area (BSA) to obtain LV mass index (LVMI), normal values of the above echocardiogram parameters according to the American Society of Echocardiography. LVDD was diagnosed according to current guidelines [20], by PW Doppler of mitral inflow and Doppler Tissue Imaging of the mitral annulus. All LVDD subjects had abnormal diastole, for all different degrees of severity. 3752 patients with arterial hypertension had a diagnosis of hypertensive cardiomyopathy [21], 550 postmenopausal patients were diagnosed with metabolic cardiomyopathy, according to well-established diagnostic criteria [22].

2.3. Exclusion Criteria

Exclusion criteria were systolic heart failure assessed by the diagnosis of left ventricular ejection fraction < 45%, wall motion abnormalities, coronary artery diseases, severe valvular and pericardial diseases, atrial fibrillation on enrolment, pulmonary hypertension estimated by tricuspid regurgitation velocity and the modified Bernoulli equation, renal failure assessed by serum creatinine > 1.2 mg/dl and major non-cardiovascular diseases as cancer or chronic lower respiratory tract disease, because these patients followed a strict disease specific follow up that could interfere with the study.

2.4. Study Design and Data Collection

A combined intervention strategy was tested; a network between patients, general practitioners, and cardiologists was established. Interventions were either delivered directly as healthcare provider supports or using modern technology, such as text messaging, e-mail and an online community. Interventions included education, adequate information to patients, a simplified scheme of treatment, and periodic adherence assessment. At the index date, doctors explained the rationale of the therapy: they described the posology and potential side effects of the therapy. The patient was educated to inform the doctor about a side effect without stopping therapy, using a dedicated h24 email service that promptly generated an alert for the doctor. The doctor answered the patients within 48 hours using clinical assessment or text messaging, or email, depending on the patient's specific problem. Medication adherence was estimated by the proportion of days covered for all classes of drugs after the index date. General practitioners used electronic prescription systems; e-prescription had several advantages: increasing the efficiency and effectiveness of prescribing and dispensing medications, reducing errors, improving prescription, more precise dosage and then preventing adverse drug reactions, and monitoring how prescription drugs are prescribed. The lack of the patient's request for the drug for the next therapeutic cycle generated an alert for the general practitioners, then the prescribers called the patients to clarify the matter of the lack of the request. Then, the pre-

scribers reprogrammed medication regimens if necessary, and re-educated patients on how to incorporate medication use into their daily living.

3. Results

Among 5857 menopausal hypertensive women, 3752 of them were affected by hypertensive cardiomyopathy (64%). Among 976 menopausal women with metabolic syndrome, 550 were affected by metabolic cardiomyopathy (56%). Non-adherent hypertensive women were 297 on 5857 (5%); nonadherent women with metabolic syndrome were 73 on 976 (7.2%). Taking into account only patients with cardiomyopathy, the rate of non-adherence was 5.2% between hypertensive women (194 patients on 3752) and 7.2% among patients with metabolic syndrome (40 on 550); on the other hand, the rate of non-adherence in the arm of postmenopausal patients without cardiomyopathy was 4.9% (103 on 2105) between hypertensive women and 7.7% (33 on 426) between patients with metabolic syndrome (**Table 2**).

4. Discussion

The main finding of our study is a low rate of non-adherence, ranged from 5 to 7% in all setting of menopausal women. A person is generally considered adherent if he or she takes between 80% and 120% of prescribed medication over a given time period [23]. Non adherence to medications has been reported in up to 50% of patients in different countries and settings [23] [24]; indeed non-adherence is a multifactorial issue and it is likely that no single strategy will be effective in all patient groups. Educational and motivational strategies are likely to be required to address intentional non-adherence, while behavioral and provider-focused strategies, such as a medication review focused on regimen simplification, are more likely to be successful in addressing unintentional non-adherence [25].

We observed an increased rate of non-adherence in women with metabolic syndrome when compared with hypertensive patients; this data was probably related to the complexity of the therapeutic scheme or to a poor consciousness of the disease. Medication regimen-related factors such as number of drugs, dosage

Table 2. Main findings of the study.

	Sample distribution	Non-adherent women	
HYPERT	5857	297	5.0%
HCMP	3752	194	5. 2%
MeTs	976	73	7.5%
MCMP	550	40	7.3%
noCMP	426	33	7.7%

PMW: postmenopausal women enrolled; HYPERT: postmenopausal women with hypertension; HCMP: postmenopausal women with hypertensive cardiomiophaty; MeTs: postmenopausal women with metabolic syndrome; MCMP: postmenopausal women with hypertensive cardiomiophaty; noCMP: postmenopausal women without cardiomiophaty.

frequency, administration instructions, and prescribed dosage forms are known to influence regimen complexity and, in turn, patient adherence. Moreover, it is possible that use of drugs interfering with the lifestyle lead patients to make intentional modifications in the dosing by either reducing the frequency of administration or spacing it with their activities. Educating patients on how to incorporate medication use into their daily living and on strategies to meet challenges to adherence could be beneficial. Another possible cause of lower adherence in this subgroup of patients is strong concern about adverse reactions to treatment. Indeed, a cross-sectional study of patients with various chronic illnesses reported that patients with greater concerns about their medications than perceived necessity had lower adherence rates [26]. On the contrary, the presence of cardiomyopathy did not affect medications' assumption, probably because, as previously reported [26], patients believed that their prescribed drug was necessary for maintaining health. Inadequate compliance is an age-old problem.

Numerous studies have demonstrated that inadequate compliance results in increased morbidity and mortality from a wide variety of illnesses, as well as increased healthcare costs [27] [28]. Patients with higher levels of health literacy have rates of adherence that are higher than patients that have low health literacy skills, in addition, health literacy interventions are effective in improving adherence to treatment. The average correlation between health literacy and patient adherence is higher in studies of patients with cardiovascular disease compared with studies of patients with other disease conditions. Perhaps because the consequences of both medication and lifestyle nonadherence in cardiovascular disease can be severe, patients may be more motivated to adhere when properly educated and given the opportunity to understand their treatment regimens [29].

If several factors have been identified as potential predictors of medication adherence, one cannot expect 'one size intervention, to fit all. In general, many of the interventions for long-term medications tend to be exceedingly complex, labor-intensive, costly, and only loosely patient-centric in design. In addition, questions remain as to how to optimally target interventions to patients in non-research settings, particularly in the current era of cost containment and staff reductions. Self-report questionnaires provide an opportunity to obtain information regarding medication adherence directly from the patient, caregiver, or doctor. However, the most important limitation is the lack of use when the patient is unaware of their nonadherent behavior. Therefore, self-reported questionnaires generally tend to overestimate adherence [16]. Recent evidence in type 1 diabetes treatment, showed that interventions targeting psychological and behavioral influences improve therapeutic adherence [30]. Typically, behavioral interventions aim to impact psychosocial and behavioral processes that will ultimately slow or pause clinical control. It is well known that psycho-social factors associated with medication adherence among older adults, hence, life events may be an important factor in adherence to prescribed medications [12]. Nevertheless, three important gaps remain in the study of behavioral interventions

to promote the management of patients with chronic disease: the development of individualized interventions, integration of evidence-based interventions in health and mental health care delivery settings, and advocacy initiatives to increase access to effective behavioral and mental health support. Mobile health technologies, particularly mobile apps, have the potential to improve medication adherence and clinical outcomes [27] but existing evidence is currently insufficient to unreservedly recommend the use of healthcare apps to improve adherence to CVD medications because of the generally small sample sizes, clinical and methodological heterogeneity between studies, and disparity in-app features, content, and delivery. Traditional patient education programs often increase patients' self-care awareness, disease knowledge, and motivation to change patient behaviors for better adherence [31]. Educating patients about their disease status and their medications can also increase patient confidence and participation to the diagnosis-care pathway [32]. Nevertheless, patient trust in physicians, patient-physician relationships, and quality of communication are more critical factors influencing patient adherence. Both patients and providers benefit from regular, ongoing feedback regarding performance in achieving commonly established treatment goals. Some patients benefit from maintaining a daily medication record of each dose taken or missed with relevant comments. The healthcare provider can then review this medication diary over the telephone or at the next clinic visit with the patient. Additional benefits include identifying potential predisposing factors for a relapse into old behavior and setting appropriate and realistic goals for new behaviors.

Our study showed that team-based care, the collaborative setting between primary care provider and cardiologist, and two types of voice messaging (educational and medication refill reminder calls), medication tailoring, and patient education, were significantly more effective in the promotion of therapeutic adherence to drugs. Patients reported that team-based care improved their comfort in asking clarifying questions, raising concerns about their medication regimen, and collaborating in developing their treatment plan. Assessing patient's adherence to medication in real-world settings can identify areas of unmet need and potential intervention opportunities to improve health outcomes.

5. Conclusion

Personalized approaches are required to address adherence barriers in target populations. This paper shows the effectiveness of a tailored combined intervention strategy in improving medication adherence in a large population of postmenopausal women affected by hypertension or metabolic syndrome. The rate of non-adherence in both settings of postmenopausal women was 7.7%, much lower than that described in the literature, mostly due to awareness and efficient connection among prescriber cardiologists, general practitioners, and patients. However, the rate of non-adherence was increased in patients with metabolic syndrome, maybe due to the complex therapeutic approach or to a poor consciousness of the disease. On the contrary, the presence of cardiomyopathy did

not affect medications' assumption, probably due to high consciousness of the disease. Therefore, in future, characterization of the nature of non-adherence could be essential before using specific interventions to significantly improve patient's adherence to medical therapy in a real-world setting. The most important point of strength of this work is the use of rigorous inclusion criteria, then we enrolled a homogeneous sample of patients. An important limitation of the study is the lack of subgroups stratification based on the pharmacological therapy: as the number of drugs and the side effects could be major components of non-adherence, in future, these results need to be put in the context of the actual therapy the population is treated with. Finally, we propose further research focused on developing innovative ideas for a collaborative setting between primary care providers, cardiologists, and patients with chronic diseases to investigate the efficacy of this method on long-term treatment outcomes and treatment adherence in clinical practice.

Conflicts of Interest

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

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Prevalence of Induced Abortion among Female Students in Selected Tertiary Learning Institutions in Gaborone City, Botswana

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Abstract

Induced abortion signifies that pregnancy has been tempered with. Abortion is the removal of an embryo or fetus weighing less than 500 grams from its mother. It can either be spontaneous (unprompted) or induced. Abortion remains one of the leading causes of maternal deaths in developing countries with induced abortion being the key cause. In 2014 from January to August, 9 abortion related deaths occurred in Botswana. There are several reasons female students in tertiary institutions resort to seeking induced abortion which include the socio-demographics like age and socio-economic factors like financial instability. Parental fears, unintended pregnancy and pressure from the partner also force females to terminate pregnancy. Induced abortion has claimed many women's lives especially in developing countries with very restrictive abortion laws like Botswana as women do not access safe abortion care services. The study intends to establish the determinants of induced abortion among female students in selected tertiary learning institutions in Gaborone City, Botswana. It concentrated primarily on determining the prevalence of induced abortion. This was a descriptive cross-sectional study using both quantitative and qualitative data collection techniques. Systematic random sampling technique was used to come up with 278 participants. Prior to commencement of data collection, all ethical and logistical prerequisites were satisfied. Informed consent was solicited from all the study participants and the purpose of the study was fully explained. A self-administered questionnaire was used to collect data. Microsoft Excel spread sheet was used to code, clean, and enter the data, which was then exported for analysis to the statistical package for social sciences version 24. Frequency distribution

tables, percentages graphs, and pie charts were used to illustrate the descriptive information. The study revealed that prevalence of induced abortion among female students in Gaborone City is 7.9%. They even suggested that induced abortion be liberalized. Age was the only socio-demographic factor associated with induced abortion with $p = 0.047$ using Chi Square test $\chi 2 = 7.609$, $df = 3$. The study findings concluded that female students resort to induced abortion as a result of pressure from both parents and male partners especially when the pregnancy is unintended. The study recommends that the abortion law in Botswana be made liberal to ease access to safe abortion care services. It also recommends that contraceptive commodities should consistently be available in public health facilities.

Keywords

Induced Abortion, Prevalence and Family Planning

1. Introduction

Induced abortion which can be categorized as either safe or unsafe refers to the interruption of a pregnancy by artificial means [1]. Globally, around 73 million induced abortions take place each year. However, nearly 1 out of 2 (45%) induced abortions are unsafe [2]. The rate of unsafe induced miscarriage is higher in underdeveloped countries, particularly in Africa, where induced abortion is prohibited [3]. Majority of the countries in Africa are low and middle income, thus high levels of unmet needs for contraception are observed which probably accounts for the increased rate of induced abortion. Induced abortion is not performed in public health institutions in Botswana, as it has the most restrictive laws on abortion in Africa. As a result, some doctors in private practice perform induced abortions, while the rest are self-inflicted or performed by other health professionals and quacks [4].

Induced abortion is amongst the most common causes of pregnancy-related deaths, contributing 7.9% of all maternal deaths worldwide [4]. Septic shock is the leading cause of mortality, followed by respiratory, cardiac and renal failure, including disseminated intravascular coagulation (DIC) [5].

Unwanted or unintended pregnancy has been demonstrated to play a significant role in unsafe induced abortions. Gaborone, Botswana's capital city, has the country's highest pregnancy rate (43 percent), with the majority of pregnancies being unplanned [6]. Similarly, teens are at a significant risk of unwanted pregnancy and, as a result, induced abortion [7]. These are found in all levels of education; primary, secondary and tertiary or higher learning institutions. Many students in tertiary or higher learning institutions view their time there as a step toward freedom from parental control, opportunity to start new friendships, as well as time to engage in sexual or romantic relationships. A study carried out by [8] showed a high rate of unintended pregnancies (52%) occurring in universi-

ties across Botswana.

However, an important strategy of curbing the high rate of induced abortion and its adverse effects in communities is through sexual and reproductive health care education. Tertiary learning institutions serve as an important setting to improve reproductive healthcare education in communities. These institutions offer opportunities to reach communities having different backgrounds both gender and socioeconomic. Moreover, students in tertiary level of education represent the active reproductive age group (≥18 years), some of whom are married, engaged to be married or even pregnant. The awareness and attitudes towards induced abortion and its determinant factors is therefore very crucial for students in tertiary institutions as they serve as a better communication channel to promote reproductive health and contribute immensely to reduction of abortion in communities.

Thus, our present study aimed at identifying the determinants of abortion among students in selected tertiary learning institutions in Gaborone City, Botswana.

2. Methods

This study was carried out in 5 selected tertiary learning institutions in Gaborone which is the capital city of Botswana. This was mixed cross sectional descriptive study with qualitative and quantitative research. The study was aimed at determining the prevalence and determinants of induced abortion among female students in 5 selected tertiary learning institutions in Gaborone City, Botswana. Multistage sampling technique was carried out to obtain calculated sample size. This was so because when the population is big and dispersed, multistage sampling may be more effective than simple random sampling. By breaking the population down into smaller, more manageable stages, it enables researchers to obtain a representative sample while requiring less time and resources for data collection. Furthermore, by choosing samples from various geographic regions or clusters, multistage sampling allows researchers to obtain a larger geographic coverage. This is especially helpful in situations where the population of interest is dispersed over a large area or when directly sampling the entire population would be impractical. Simple random sampling technique was used to select institutions providing hostel accommodation. Simple random sampling technique was used to pick 30% of the institutions with female hostels. Systematic random sampling technique was used to identify the respondents in the rooms. This was because each individual in the population has an equal probability of being chosen, guaranteeing that the sample fairly represents the population. This lessens the possibility that the sample selection procedure will be biased. Moreover, in comparison to other sampling techniques, it is comparatively simple to comprehend and use. There are no complex procedures involved; instead, elements are chosen at random, which makes it appropriate for a variety of research settings. To determine the sample size,

Fishers *et al.* second correction formula was used to achieve sample of 278 respondents from 5 tertiary learning institutions since the population estimate was <10,000.

Responses from respondents were coded, entered into a Microsoft excel sheet then exported to SPSS version 24 for analysis. Descriptive statistical analysis of data involving frequency, percentages, and graphical presentations were used to describe socio demographic features of respondents. The prevalence of induced abortion among female students was presented using a table. Inferential statistical analysis involving multivariate logistic regression was used to analyze attitude, level of knowledge and factors relating to induced abortion. Relationships among the study were tested at 95% confidence interval ($p < 0.05$) (Table 1).

3. Results

The study aimed at sampling 260 participants however, 278 respondents were approached and they all consented. The study participants were mostly aged 17 - 26 years 216 (77.7%), 27 - 36 years 48 (17.3%), 36 - 47 years 9 (3.2%) and 47 - 56 years 5 (1.8%). Majority of the study participants were in year 2 of study 72 (25.9%), year 3 70 (25.2%) and year 1 68 (24.5%). Most of the respondents were unemployed 249 (89.6%) and majority of the employed respondents had formal kind of employment 17 (58.6%). Majority of the study participants reported to be Christians 246 (88.5%). Most of the participants were not married 231 (83.1%). Majority of the respondents have engaged in sexual activity 212 (76.3%). Most had their sexual debut from the age of 18 years and beyond 163 (76.9%) while 49 (23.1%) have had their sexual debut at the age of 18 years and below (Table 1).

More than half of the respondents who have engaged in sexual activity 126 (59.4%) have never been pregnant and only 86 (40.6%) have been pregnant. More than half of the participants who have been pregnant, have been so once 47 (54.7%) while 29 (33.7) have been pregnant twice. Significant proportion of

Table 1. Prevalence of induced abortion among the respondents.

Variable	Category	n (%)
What was the nature of the abortion	Spontaneous (miscarriage)	9 (3.2)
	Induced (use of substances or devices)	22 (7.9)
What period of pregnancy did you undergo abortion	1month	4 (18.2)
	2 months	3 (13.6)
	3 months	8 (36.4)
	Above 3 months	7 (31.8)
What year of study did you undergo induced abortion	After High school (after Form 5 but before Year 1)	8 (57.1)
	Year 1	6 (42.9)

the participants who have ever been pregnant reported to have experienced an abortion 31 (36.0%) and 55 (64%) have not experienced it. Most respondents experienced abortion once 29 (93.5%) while 2 (6.5%) experienced it 2 or more times (Table 1).

Most abortions were induced 22 (7.9%) and were equally induced by both health workers 11 (50.0%) and non-health workers 11 (50.0%). Only 9 (3.2%) were spontaneous abortions. Most of the induced abortions were carried out at home 11 (68.2%). These induced abortions were mostly done at 3 months' gestation 8 (36.4%) and 7(31.8%) were done above 3 months gestation. Majority 8 (57.1%) of the induced abortions were done after high school (after Form 5 but before Year 1) (Table 2).

Prevalence of induced abortion among the respondents: Among the respondents, 9 (3.2%) respondents experienced spontaneous abortion while 22 (7.9%) experienced induced abortion. The abortions were equally induced by both health workers 11 (50.0%) and non-health worker 11 (50.0%). Most of the induced abortions were carried out at home 11 (50%) while 7 (31.8%) were carried out at the pharmacy/chemist and 4 (18.2%) were done at the hospital. The induced abortions were mostly done at 3 months' period of pregnancy 8 (36.4%) and before year 18 (57.1%) and 6 (42.9%) were in year 1. A significant number 7 (31.8%) had induced abortion while above 3 months pregnant, 4 (18.2%) were a month pregnant and only 3 (13.6%) were 2 months pregnant (Table 2).

The purpose of the study was to ascertain how socio-demographic factors affected induced abortion among the respondents. The demographic factors were age, level of education, employment, religion and conjugal status. There is significant association between age category and induced abortion among students in tertiary learning institutions in Gaborone, Botswana ($p < 0.05$) (Table 2).

4. Discussion

Despite the restrictive law on abortion in Botswana, the study found that out of 86 (40.6%) respondents who have been pregnant before, 31 (36%) have experienced an abortion and among them, 22 (7.9%) have experienced induced abortion thus making prevalence of induced abortion among female students in the 5 selected tertiary learning institutions in Gaborone City to be 7.9%. Similar findings were revealed by a study conducted in preparatory school student in Guraghe Zone, Southern region, Ethiopia where lifetime prevalence of induced abortion was 13.61%.

Majority of the respondents who have ever experienced abortion, 93.5% of them reported to have experienced it only once. Amongst those who had abortion half of them had induced abortions which were done either by health workers or non-health workers using Misoprostol tablets or pills sold in the chemist/pharmacy. The findings comply with a study done in Kinshasa which has shown that most women nowadays use tablets/pills to induce abortion by themselves or by the help of a health worker using Misoprostol which is readily

Table 2. Socio-demographic factors associated with induced abortion among students in tertiary learning institutions in Gaborone, Botswana.

Variable	Category	Induced Abortion		Chi²/Fisher's exact
Age Category	17 - 26 years	2 (22.2%)	16 (72.7%)	$\chi^2 = 7.609$ $P = 0.047$ df = 3
	27 - 36 years	5 (55.6%)	3 (13.6%)	
	36 - 47 years	1 (11.1%)	2 (9.1%)	
	47 - 56 years	1 (11.1%)	1 (4.5%)	
Level of Education	Year 1		4 (18.2%)	$\chi^2 = 8.115$ $P = 0.081$ df = 4
	Year 2		5 (27.2%)	
	Year 3	2 (22.2%)	3 (13.6%)	
	Year 4	3 (33.3%)	8 (36.4%)	
	Post graduate	4 (44.4%)	2 (9.1%0	
Employment	Yes	5 (55.6%)	55 (22.7%)	χ2 = 3.15 P = 0.09 df = 1
	No	4 (44.4%)	17 (77.3%)	
Type of employment	Formal	4 (80.0%)	2 (40.0%)	$\chi^2 = 1.667$ $P = 0.262$ df = 1
	Self-employed	1 (20.0%)	3 (60.0%)	
Religion	Christian	7 (77.8%)	18 (81.8%)	$\chi^2 = 0.714$ $P = 1.000$ df = 2
	Other religion followers		1 (4.5%)	
	Atheist (does not believe in God)	2 (22.2%)	3 (13.6%)	
Conjugal Status	Married	4 (44.4%)	3 (13.6%)	$\chi^2 = 3.673$ $P = 0.272$ df = 2
	Single	4 (44.4%)	13 (59.1%)	
	Cohabitation	1 (11.1%)	6 (27.3%)	
At what age did you start engaging sexual activity	<18	3 (33.3%)	7 (31.8%)	$\chi^2 = 0.007$ $P = 0.625$ df = 1
	≥18	6 (66.7%)	15 (68.2%)	
Employment of guardian	Formal	7 (77.8%)	10 (45.5%)	$\chi^2 = 3.735$ $P = 0.173$ df = 2

available in the market [9]. This is a drug registered to be used in obstetric practice, as a life-saving drug, however misoprostol-related self-induced abortion is becoming more common in many communities [10].

Similarly, the availability of abortifacient tablets like Misoprostol makes it easy for women including students to easily access it for termination of unintended pregnancy [11]. The study findings have shown that among 36.0% of respondents who have experienced pregnancy loss, 87.1% used tablets/pills to terminate the pregnancy. Other 12.9% used instruments like boiled match sticks and poi-

sonous tree branches which is termed least safe. This is consistent with the findings by 20 revealing that in a study on the incidence of abortion and unintended pregnancy in India, 2015, the prevalence of induced abortions done outside the medical facilities, 73% of abortions were performed using medication, while 5% were performed using means other than medication abortion. The induced abortion was done at 3 months gestation which is similar to the findings of a study by [12] which indicated that the type of method or instrument used for induced abortion, the gestational age at which induced abortion is done as well as the person doing it determine whether it is least safe or less safe [13]. With the respondents the induced abortion is least safe because it was done by both health workers and non-health workers mostly using the medicines and not invasive objects [14].

Even though the abortion law is restrictive in Botswana, the majority of induced abortions were done at home after high school but before starting year 1 in tertiary institutions. This is the period when students (males and females) are waiting for high school results as well as to be placed to tertiary learning institutions of their choice. These findings of high prevalence of induced abortion are maintained in the study by 3 among women in Ghana which revealed that 64.1% of the respondents had unsafe induced abortions [15].

Restrictive abortion laws do not help in reducing the rate of induced abortion in any country. According to the study findings, prevalence of induced abortion was high despite the restrictive abortion law in Botswana [16]. These findings are consistent with the ones in which a cross-sectional retrospective study conducted in four hospitals in Botswana by [16] which exposed that though abortion is verboten in the country, the rate of its complications and deaths were quite significant. The same study revealed a total of 9 deaths due to abortion related outcomes which occurred from January to August 2014, yielding a 1.5% case fatality rate [17].

Other similar findings were found in a publication by [17] which revealed that restricting access to abortion care services does not always deter women from getting one, but rather it does a lot to decide the morbidity and mortality associated with it because so many women turn to risky, covert procedures. Though induced abortion amongst the respondents was done at home, it was done at 3 months (12 weeks) gestation which is said to be safer [18]. These findings are consistent with a study by [19] which indicated that termination of pregnancy using medicines or tablets was usually done when the gestational age is around 9 weeks after the woman's last normal menstrual period after which vacuum aspiration is employed to evacuate the uterus [20].

The study explored what could be the hindrance to prevent induced abortion and several interventions were revealed by the qualitative data and it was evident that restrictive abortion laws play a critical role in the high prevalence of induced abortion. The results are in line with the findings of a study by [20] where it was indicated that restrictive laws do not stop women from doing induced abortion but rather play a pivotal role in increasing morbidity and mortality. [21] continued to show that women are not free to access safe abortion care ser-

vices as they can be prosecuted if found to have done induced abortion. When the abortion law is liberal, there is reduced numbers of induced abortion as well as less abortion related complications [22]. Despite this, abortifacients like Misoprostol are readily available in the market for females to easily access. Induced abortion is stigmatized in many communities as those who have done it are labelled as murderers [22].

Repeated stockouts of contraceptive commodities play an important role in the occurrence of induced abortion. The findings from qualitative data exposed that in most cases there were repeated stock outs of contraceptives (family planning commodities) which left female students with little or nothing to use except to engage in unprotected sexual activities resulting in unintended pregnancy. It was revealed that expanding the use of consistent and effective contraceptives in Eastern Europe led to a significant drop in induce abortion rates [23].

5. Limitations and Delimitation

The study was conducted in 5 selected tertiary learning institutions in Gaborone City, Botswana; 3 parastatals (both government and private owned) and 2 public institutions. These tertiary learning institutions were chosen because they provide female students with dormitories. The institutions were all located in and around (outskirts) of Gaborone City, making them accessible to the researcher. The study was conducted at a time when year 1 students were just starting their First Semester orientations and, in some institutions, continuing students were sitting for continuous assessment examinations and having laboratory practical sessions which posed a challenge to collect data during working hours. Nonetheless, data collection was achieved by arranging with housekeepers, guidance and counselling teachers) and ultimately student representative council (SRC) members to collect data even in the late afternoon after examinations and registration processes. Tertiary learning institutions which were purely private owned declined to be used as study sites citing the sensitivity of the study topic as an interference with one's privacy hence the parastatal ones were then used. Owing to the fact that in Botswana induced abortion is restrictive and considered a sensitive topic, some respondents might have not been free/genuine to give information about themselves.

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Declaration

The Government of Botswana through Ministry of Health funded my studies.

More so, this thesis is my original work and has not been presented for a degree in any other university. Additionally, written consent was sorted from each tertiary institute of learning under study. Throughout the study activity, the standards of informed consent, voluntary participation, and confidentiality were upheld in each of the sampled institutions. The respondents' identities were not revealed, thus ensuring anonymity. Participation in the survey was entirely on voluntary basis, and subjects were informed that they had the liberty to opt out at any time without consequences.

Conflicts of Interest

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

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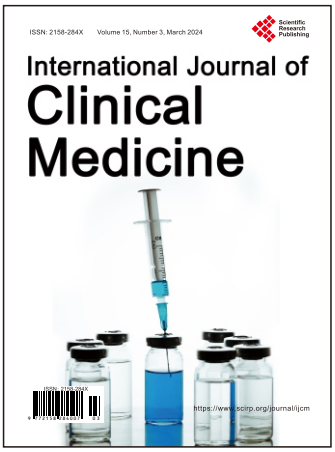

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