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Effect of Repetitive Transcranial Magnetic Stimulation on Change in Delta Theta Alfa Beta Ratio (DTABR) and Motor Function in Ischemic Stroke Patients

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Abstract
Background: Stroke is the leading cause of long-term disability worldwide. The electroencephalography (EEG) of ischemic stroke patients is a slow background and the quantitative electroencephalogram (qEEG) shows an increased delta+theta/alpha+beta ratio (DTABR). Disability can be assessed using a Fugl Mayer Motor Assessment (FMA). In this study, we will examine the effect of Repetitive transcranial magnetic stimulation (rTMS) on changes in DTABR and assess motor function improvement in ischemic stroke patients with unilateral brain lesions. *Methods:* Thirty patients were divided into 2 groups. The first group received standard stroke therapy and gave rTMS intervention. The second group received only standard stroke therapy. All patients recorded using a EEG recorder and the results will be converted into qEEG. All samples will also be assessed for motor function using FMA before and after the intervention. The qEEG results obtained the absolute value of the power of each brain wave which we then calculated DTABR before and after treatment. *Results:* There was a greater decrease in DTABR in the treatment group when compared to the control group on the EEG electrodes Cz ($p=0.029$), C3 ($p=0.048$), C4 ($p=0.004$), Pz ($p=0.015$) and total DTABR ($p=0.011$) and greater motor improvement in the treatment group when compared to the control group $p<0.001$. In the Spearman's test there is a relationship between changes in DTABR and FMA with p value = 0.001. *Conclusion:* There is an increase in motor function associated with a decrease in DTABR in patients with ischemic stroke with unilateral lesions after rTMS intervention

Keywords: Stroke Ischemic, Repetitive Transcranial Magnetic Stimulation, Fugl Mayer Assesment, Quantitative Electrocephalogram

1. Introduction

Stroke is the second leading cause of death after ischemic heart disease and is the leading cause of long-term disability worldwide (Coupland et al., 2017; Benjamin et al., 2019). In 2019, the worldwide incidence of stroke was around 12.2 million new cases with 7.63 million of whom were people with ischemic stroke (GBD, 2020). In

Indonesia alone, the prevalence of stroke is quite high, namely 10.9% per 1000 population. This figure increased when compared to the Basic Health Research (Riskesdas) in 2013 which was 7%. The prevalence of stroke in 2018 was highest in East Kalimantan (14.7%) and the lowest in Papua Province (4.1%) (Kemenkes, 2018).

In 2016, 60% of new cases of ischemic stroke patients were people aged <60 years and about 7% were under 44 years of age (Lindsay et al., 2019). According to the American Heart Association, nearly 75% of stroke patients experience disability and 15-30% of stroke survivors have a severe and permanent level of disability (Go et al., 2014). Disability in stroke patients can be in the form of motor weakness, sensory disturbances, language disorders, memory disorders and emotional disturbances depending on the area where the vascularization disorder occurs (NINDS, 2020). Motor weakness causes many problems, including causing difficulty in walking. or activity and may cause the patient to become immobilized. Immobilization can cause joint pain, limited range of movement (ROM), joint stiffness, muscle atrophy, muscle spasm, shoulder pain, knee flexion contractures, muscle weakness and footdrop (Elmasry et al., 2015). in stroke patients. Management of stroke patients can be in the form of preventive, promotive, curative and rehabilitative. Preventive and promotive efforts are usually carried out at first-level health facilities in the form of discovery, early detection and control of stroke risk factors (Kemenkes, 2013). Curative management is generally carried out in hospitals, acute ischemic stroke management can be in the form of recanalization of blood vessels such as recombinant tissue plasminogen activator (rTPA). with thrombolytics and mechanical thrombectomy (Powers et al., 2019). Therapy using rTPA and mechanical thrombectomy gave excellent clinical outcomes (Prawiroharjo, 2017), but this procedure also has limitations including the limited time of administration, limited infrastructure such as the availability of medical personnel and imaging equipment is lacking, geographical conditions, and community factors such as low levels of knowledge cause the management of acute ischemic stroke not to be maximal (Tangkudung, 2020). Post-acute stroke patients with motor weakness are generally given repetitive physical exercise, physical activity with the help of technology such as the use of robots and virtual reality, as well as noninvasive brain stimulation in this case the use of Transcranial Magnetic Stimulation (TMS) which is intended to stimulate neuroplasticity (Edwards, 2008).

rTMS affects synaptic plasticity in several ways, by inducing increased release of neurotransmitters such as dopamine, stimulating the growth of glial cells and preventing neuronal cell death. Stimulation of the motor cortex using rTMS can increase the release of the neurotransmitter dopamine in the nucleus accumbens (Strafella, 2003). rTMS can activate the glutamate system, activation of the glutamate system will activate N-methyl-D-aspartate (NMDA) receptors which will affect brain neuroplasticity (Moretti et al., 2020). Stimulation produced by rTMS also helps in the reperfusion process by increasing adenosine triphosphate. ATP) in the striatum of ischemic cerebral hemispheres (Kim & Yim, 2018). The combination of physical exercise and rTMS when performed simultaneously can induce neuroplasticity well and provide better motor improvement results than when administered alone (Yang et al., 2020). The rTMS intervention has also been shown to affect wave activity. brain associated with changes in neuroplasticity, nerve transmission, and blood flow to the brain (Zhong et al., 2021).

Electoencephalography (EEG) can record the electrical activity of the brain which is described with brain waves. When cerebral blood flow (CBF) decreases, brain tissue ischemia occurs and an abnormal EEG picture is obtained in the form of an increase in slow wave activity (delta and theta) and a decrease in fast waves (alpha and beta) (Hirsch et al., 2021; Jordan, 2004). Abnormalities that appear can be an increase in the delta/alpha ratio (DAR), an increase in (delta+theta)/(alpfa+beta) ratio (DTABR) and changes in brain symmetric index (BSI) are common in stroke patients (Finnigan et al., 2016; Sheorajpanday et al., 2011). DTABR and alpha relative power are quantitative indices. Quantitative Electroencephalography (qEEG) is the best in determining stroke outcome. DTABR is said to be associated with cerebral perfusion and oxygen metabolism. Motor outcomes were assessed using the modified Ranking Score (mRS) and a unidirectional relationship was found between low mRS and low DTABR (Bentes et al., 2018). In general, the DTABR value is said to be normal if it has a value < 1 (Finnigan & Putten, 2013).

The protocol of administering rTMS stimulation with a combination of high frequency on the ipsilateral lesion and low frequency on the contralateral lesion is a common protocol (Zhong et al., 2021). Administration of rTMS with a frequency of excitation in the area of the motor cortex ipsilateral to the lesion and a frequency of inhibition in the contralateral lesion can increase cerebral blood flow (CBF). High-frequency stimulation (>5 Hz) leads to

increased alpha and beta wave activity (Thut et al., 2011) and can decrease delta activity in patients with schizophrenia (Kamp et al., 2016). Administration of rTMS with a frequency of 10 Hz at the Cz EEG electrode area can reduce delta activity at the lesion site which may play a role in clinical improvement (Zhong et al., 2019). Administration of rTMS with a frequency of 1 Hz to the motor cortex, increased the absolute power of delta waves in normal subjects (Qiu et al., 2019). In this study, the researcher wanted to see the effect of giving rTMS on DTABR and motor function of ischemic stroke patients with unilateral lesions.

2. Method

2.1 Research Design

This study is an experimental study with a pre-test post-test control group design that aims to compare changes in DTABR using quantitative EEG and changes in motor function of post-ischemic stroke patients in the group receiving standard ischemic stroke therapy with a combination group between standard ischemic stroke therapy and repetitive transcranial magnetic stimulation (rTMS).

2.2 Research Location and Time

The research was conducted at the Neurology Polyclinic of Dr. Central General Hospital. Wahidin Soedirohusodo, from October 2021 to January 2022, Makassar. Population and Sample. The study population was post-ischemic stroke patients who visited the Neurology Polyclinic Iof Wahidin Sudirohusodo Hospital from October 2021 to January 2022. The study sample was determined by consecutive sampling, i.e. all subjects who came and met the research criteria were included in the study until the required number of subjects was met. Samples were taken from the study population based on the order of admission to the hospital (Consecutive sampling).

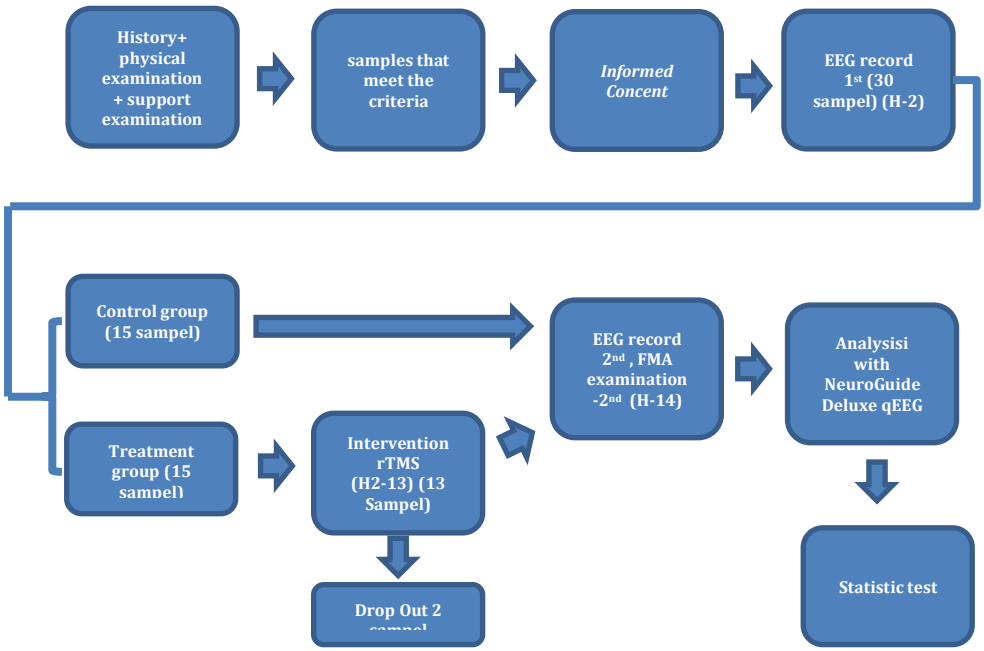
2.3 Population and Sample

Inclusion criteria in this study were post-ischemic stroke patients diagnosed based on history, physical examination and CT scan results without contrast, age 35-65 years, first attack, onset of more than 14 days and less than 3 months, supratentorial lesions, weakness moderate - very severe motor skills based on the FMA score, aware, cooperative and willing to be included in this study by signing an informed consent. The exclusion criteria were having received rTMS therapy, patients with contraindications to the use of TMS; use of cardiac pacemakers, cochlear implants and use of metal artifacts and patients at risk or history of seizures. The criteria for drop-out patients in this study were patients who did not participate in the electroencephalography recording session, the patient did not participate in the entire repetitive Transcranial Magnetic Stimulation session, the patient died, the patient withdrew as a sample, due to certain reasons.

2.4 Data Collection

All subjects were given an explanation about the study, if they agreed they were asked to sign an informed consent. Subjects were divided into two groups, namely treatment and control which were determined based on the time of arrival. Subjects who came in the order of 1-15 were the treatment group and 16-30 were the treatment group. All subjects received standard therapy, namely medication and rehabilitation (according to the ischemic stroke management protocol at Dr. Wahidin Sudirohusodo Hospital) and the treatment group was added to rTMS stimulation. On the first day of the visit, all selected subjects were assessed using the FMA, which can check the motor strength of the upper and lower extremities. On day 2, all subjects were recorded for 5 minutes of EEG. Furthermore, rTMS stimulation was given with a combination of high frequency (HF) of 10 Hz on the ipsilateral lesion and low frequency (LF) of 1 Hz on the contralateral lesion. The rTMS was given 10 times, 5 times consecutively every day, then 2 days apart and then 5 days in a row. On the 14th day, all subjects were again assessed using FMA and EEG recordings. The results of the EEG recording will be processed using NeuroGuide Deluxe qEEG software and converted into quantitative electroencephalogram (qEEG) data. Then, the ratio (delta+theta)/(alpha+beta) (DTABR) was calculated on the EEG electrodes Cz, C3, C4, Pz, P3 and P4, and DTABR total. The total DTABR is the total absolute power value of each wave on all electrodes installed (19

electrodes). In this study, the Fugl-Mayer Assessment Test was used to assess the level of motor recovery in ischemic stroke patients. There are five domains that are assessed by the Fugl-Meyer scale, namely, 1) Motor function (maximum score in the upper extremity is 66, for the lower extremity 34), 2) Sensory function (maximum score is 24), 3) Balance (maximum score is 14), 4) Joint range of motion (maximum score is 44), 5) Joint pain (maximum score is 44). In the application of FMA, each of these five FMA domains can be separated according to the purpose of the assessment. Motor domain assessment includes assessment of shoulder, elbow, forearm, wrist, hand, hip, knee and ankle movement, coordination and reflexes. The FMA reliability value for stroke patients is quite high with an intraater value of r=0.98-0.99 and a retest r=0.97. For the upper extremities, the intraater value r = 0.995-0.996 and for the lower extremities the intraater value r = 0.96. The maximum value for upper and lower extremity FMA examination is 100, then divided into 4 criteria. Very severe criteria if the FMA score is 0-35, severe 36-55, moderate 56-79 and mild >79. During data collection there were 2 samples in the treatment group that had to be excluded because they met the drop-out criteria. The sample collection method can be seen in Figure 1.



2.5 Repetitive TMS

The rTMS intervention was given in 2 cycles. Each cycle consists of 5 consecutive days, then a pause of 2 days, followed by a second cycle for 5 consecutive days. rTMS was performed in the M1 area, which is the primary motor area. On the ipsilateral lesion was given rTMS with a frequency of 10 Hz while on the contralateral lesion was given rTMS with a frequency of 1 Hz

2.6 Analysis Data

All data will be analyzed using IBM© SPSS© 25 (New York, United States). To assess the distribution of data, the Shapiro-Wilk test is used. For normal data distribution, Paired T test and Independent T test were used, while for abnormal data distribution, Wilcoxon test and Mann Whitney U test were used. The hypothesis is said to be significant if the p value <0.05 is obtained. The correlation test used Spearman's test.

2.6.1. Research permit and Ethical Eligibility

In carrying out this research, all research subjects were given an explanation of the aims, objectives and uses of the research, including the risks that could occur. After receiving an explanation, the subject signed the Research Participant Approval Letter and every action was carried out with the permission and knowledge of the subject

through an informed consent form. This research has also been approved by the health research ethics committee of the Hasanuddin University RSPTN RSUP Dr. Wahidin Sudirohusodo Makassar with number 712/UN4.6.4.5.31/PP36/2021.

2.7 Results

This research was conducted on 30 subjects which were divided into 2 groups. The first group consisting of 15 samples was the treatment group that received rTMS intervention while the second group of 15 subjects was the control group who only received standard stroke therapy. Demographic data and patient characteristics can be seen in Table 1. Table 1 shows there is no significant difference between the two groups based on the FMA category.

Table 1: Demographic data of research sample

Charastericts		Treatment			Control			P
		(n)	%	Mean	(n)	%	Mean	
Age	36-45 years old	3	20	52.26 (SD ±8.05)	3	20	51.93 (SD ±6.91)	0.904[a]
	46-55 years old	6	40		9	60		
	56-65 years old	6	40		3	20		
Onset Stroke (day)		15	-	30.86 (SD ±23.75)	15	-	22.46 (SD ±11.03)	0.526[b]
Gender	Man	11	73.3	-	11	73.3	-	1.00[c]
	women	4	26.7	-	4	26.7	-	
Risk Factor	HT	9	60	-	11	73.3	-	0.141[c]
	DM	0	0	-	0	0	-	-
	HT+DM	6	40	-	4	26.7	-	0.699[c]
Lesion location	Right Hemisfer	10	66.7	-	9	60	-	0,705[c]
	Left Hemisfer	5	33.3	-	6	40	-	
FMA Category	Very severe	6	40	-	5	33,3	-	0,264[c]
	Severe	8	53,3	-	8	53,3	-	1.00[c]
	Moderate	1	6,7	-	2	13,4	-	0,685[c]

Source: Primary Data a) independent T test, b) Mann-Whitney test, c) Chi-Square test. FMA: Fugl Mayer

2.8 Assesment Test

Table 2 shows the changes in DTABR before and after therapy in the control and treatment groups. In the treatment group, all EEG electrodes were Cz (p=0.019), C3 (p=0.012), C4 (p=0.007), Pz (p=0.004), P3 (p=0.032), P4 (p=0.003) and total DTABR. (p=0.003) experienced a significant decrease in DTABR between before and after treatment. Meanwhile, in the control group, only the EEG electrodes Pz (p=0.017) and P4 (p=0.001) experienced a significant decrease in DTABR.

Table 2: DTABR Score Before and After Therapy

EEG Electrode	Treatment						Control					
	Mean	SD	Median	Min	Max	P	Mean	SD	Median	Min	Max	P
Cz_Pre	2.21	1,52	1,98	0,33	5,87	0,019**	1.35	0.80	1,11	0,4	3,04	0,681**
Cz_Post	1.45	0.81	1,34	0,27	2,71		1.18	0.66	1,05	0,35	2,34	
C3_Pre	2,25	1,55	1,89	0,30	6,17	0,012**	1.49	1.37	1,04	0,5	5,18	0,109*
C3_Post	1.4	0.8	1,39	0,24	2,76		1.18	0.83	0,7	0,46	3,15	
C4_Pre	2.07	1.5	1,83	0,30	5,88	0,007**	1.43	0.90	1,1	0,31	3,18	0,154**
C4_Post	1.22	0.76	1,21	0,19	2,59		1.31	0.83	1,17	0,31	2,82	
Pz_Pre	2.15	1,33	1,83	0,29	5,38	0,004**	1.44	0.92	1,15	0,37	3,22	0,017*
Pz_Post	1.25	0.62	1,22	0,29	2,21		1.18	0.77	0,93	0,34	2,61	
P3_Pre	1,92	1,17	1,86	0,29	4,46	0,032**	1.32	1.14	1	0,26	4,29	0,069*
P3_Post	1.37	0.84	1,14	0,26	2,75		1.06	0.71	0,72	0,24	2,62	

P4_Pre	1,96	1.55	1,34	0,28	5,61	0,003*	1.48	1.15	1,08	0,12	3,69	0,001*
P4_Post	1.25	0.79	1,31	0,26	2,74		1.10	1.05	0,73	0,06	2,56	
DTABRtpre	2,11	1,12	2,17	0,54	4,59	0,003**	1,47	0,93	1,22	0,43	3,9	0,054**
DTABRtpost	1,39	0,7	1,16	0,34	2,54		1,21	0,66	0,96	0,39	2,36	

*Source: Primary Data, *Wilcoxon test, **Paired t test*

Table 3 shows the comparison of changes in DTABR in the treatment group and the control group. There was a significant difference in DTABR scores on the electrodes Cz (p=0.029), C3 (p=0.048), C4 (p=0.004), Pz (p=0.015) and total DTABR (p=0.011) when compared between the treatment and control groups. The decrease in the treatment group was greater than the control group. This may reflect the effect of rTMS on changes in DTABR where the changes were greater in the treatment group compared to the control group at the Cz, C3, C4, Pz and DTABR total EEG electrodes.

Table 3: Comparison of DTABR Scores of Treatment and Control Group

Variable	Group	Δ Mean (SD)	Median	Min	Max	Significant
delta_Cz	Treatment	0,76 (±1,02)	0,35	-0,06	3,41	0,029*
	Control	0,17 (±0,33)	0,04	-0,32	0,8	
delta_C3	Treatment	0,85 (±1,03)	0,82	-0,15	3,46	0,048*
	Control	0,32 (±0,72)	0,05	-0,43	2,58	
delta_C4	Treatment	0,85 (±0,95)	0,7	-0,08	3,46	0,004*
	Control	0,11 (±0,28)	0,02	-0,2	0,7	
delta_Pz	Treatment	0,90 (±0,90)	0,57	0	3,17	0,015*
	Control	0,25 (±0,37)	0,07	-0,1	1,05	
delta_P3	Treatment	0,54 (±0,81)	0,4	-0,59	2,26	0,279*
	Control	0,26 (±0,51)	0,13	-0,46	1,67	
delta_P4	Treatment	0,71 (±1,03)	0,33	0	3,34	0,489*
	Control	0,38 (±0,49)	0,25	0,01	1,68	
Total delta_DTABR	Treatment	0,72 (±0,69)	0,54	0,14	2,36	0,011*
	Control	0,26 (±0,47)	0,04	-0,12	1,54	

*Source: Primary Data, *mann Whitney U test*

Table 4 shows changes in FMA scores before and after therapy. In the control and treatment groups, there were significant differences in motor function after therapy. This is indicated by the significance value of motor function before and after therapy in the treatment group and the control group having a p value = 0.001 (<0.05).

Table 4: FMA Score Before and After Therapy

	Treatment					Control				
	Mean (SD)	Median	Min	Max	p	Mean (SD)	Median	Min	Max	p
FMA_pre	36,23 (±19,23)	39	8	63	0,001*	39,4 (±22,87)	41	8	79	0,001*
FMA_post	62,92 (±19,37)	65	29	88		53,2 (±21,89)	56	15	84	

*Source: Primary Data, *Paired t test,**Wilcoxon test **description :**FMA : Fugl Mayer Assesment Test, FMA_UE : Fugl Meyer Assesment Test Upper Extremitiy. FMA_LE : Fugl Meyer Assesment Test Lower Extremitiy.*

Table 5 shows a comparison of changes in motor function between the treatment group and the control group. There was an increase in the difference in FMA scores almost two times greater in the treatment group with an average value of 26.69 (±5.48) compared to the control group with an average value of 13.8 (±6.88). There was a significant difference between the treatment and control groups with p value < 0.001 where the change was greater in the treatment group than the control group.

Table 5: Comparison of FMA Scores in the Treatment and Control Groups

Group	Δ Score (mean±SD)	Median	Min	Max	p
Treatment	26,69 (±5,48)	24	19	35	
Control	13,8 (±6,88)	16	7	29	<0,001*

*Source: Primary data, *independent t test*

Table 6 shows the relationship between changes in total DTABR and an increase in motor function. Total DTABR and motor function were tested using Spearman's correlation test, it was found that there was a significant relationship between changes in total DTABR and changes in motor function with p value = 0.001. The correlation is strong positive which is indicated by the value of .584. This means that the greater the decrease in DTABR, the greater the increase in motor function (FMA score).

Table 6: Analysis of the relationship between total DTABR and the improvement of motor function in the treatment and control groups

Spearman's rho		delta DTABRtotal	delta FMA
delta DTABRtotal	Correlation Coefficient	1.000	.584**
	Sig. (2-tailed)	.	.001
	N	28	28
delta FMA	Correlation Coefficient	.584**	1.000
	Sig. (2-tailed)	.001	.
	N	28	28

*Source: Primary Data, *Spearman's correlation test*

3. Discussion

This study aims to determine the effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) with high frequency (10 Hz) on the ipsilateral lesion and low frequency (1 Hz) on the contralateral lesion to changes in the Delta+Theta/Alfa+Beta (DTABR) ratio and motor function improvement. in ischemic stroke patients with motor impairment.

In this study initially there were 30 samples divided into 2 groups, namely the treatment group (n=15) and the control group (n=15). The treatment group was the group that received 2 cycles of rTMS intervention. The control group was the group that received standard stroke therapy in the form of drugs and physiotherapy. In its development in the treatment group there were 2 samples that dropped out because the patient resigned, so that the total number of samples at the end of the study was 28 samples where the treatment group (n = 13 samples) and the control group (n = 15 samples).

Various previous studies have shown that the incidence of stroke will increase with age (Schwamm et al., 2017). Age is the strongest risk factor for stroke and this stroke risk will double every decade over age 55 (Caplan, 2016). In this study, the highest age group was 46-55 followed by 56-65 years. The most important predictors of outcome in the acute phase of stroke were stroke severity and patient age. Stroke severity can be assessed clinically, based on various parameters of neurological impairment (eg, mental changes, motor deficits, language, visual field deficits, behavior) and the size and location of the infarct on neuroimaging by MRI or CT scan (Konig et al., 2008). In old age, patients experience improvement. but at a slower pace and overall age has a relatively small impact on motor improvement in stroke patients (Teasell & Hussein, 2020).

The incidence of stroke in men is higher than in women (Perdossi, 2011). As the age increases, the incidence of stroke in women increases. A population-based study in Sweden found that the incidence of stroke in women was 60% lower than that of men at the age of 55-64 years, but at the age of 75 women had a 50% higher incidence than

men (Lofmark & Hammarstrom, 2007). In this study the number of male subjects as many as 22 people (73.3%) and 8 women (26.7%).

Hypertension is the second strongest risk factor after age and people with hypertension are about 3 or 4 times more likely to have a stroke (Chobanian et al., 2003). A strong association between hypertension and stroke has been associated with a strong effect of hypertension on the cerebral circulation. In cerebral vessels, hypertension is known to cause hypertrophy of the vessel walls and a reduction in the diameter of the external lumen of the vessels. In addition, hypertension alters the ability of endothelial cells to release vasoactive factors and increases systemic and cerebral arterial constrictor tone (Iadecola & Gorelick, 2004). All samples in this study had hypertension risk factors and 10 of them had hypertension and diabetes mellitus. In the demographic data, there were no significant differences between the treatment group and the control group in age, gender, risk factors and lesion location.

Brain waves are associated with neuronal activity in the brain that reflects the process of excitation and inhibition of nerve cells (Rabiller et al., 2015). The increase in excitability of nerve cells is described by an increase in the neuronal population as well as when the nerve cell is inhibited, which occurs is a decrease in the neuronal population (Jensen & Mazaheri, 2010). The main factor that inhibits functional recovery after stroke is a change in synaptic function, namely a decrease in excitability or a decrease in excitability in the part of the brain affected by stroke and interhemispheric imbalance. Poststroke recovery is promoted by reducing transcallosal inhibition in the affected hemisphere and inhibition of excitability from the normal hemisphere. rTMS as noninvasive brain stimulation can be used as an additional therapeutic option for motor function recovery after stroke because it can regulate cerebral cortex excitability and nerve plasticity depending on the stimulation parameters used. rTMS can also induce synaptic plasticity and alter interhemispheric interactions (Fisicaro et al., 2019).

The working principle of TMS is to produce an induced current that can affect brain metabolism and nerve electrical activity. Administration of rTMS with a frequency of 1 Hz can inhibit the cortex while >1 Hz can excite the cerebral cortex (Lewis et al., 2016). Based on this principle, the treatment group in our study apart from drug therapy was also given rTMS stimulation with a combination of high frequency (10 Hz) on the ipsilateral lesion and low frequency (1 Hz) contralateral to the lesion. With this combination, we expect that on the side of the lesion will experience cortex excitation, while on the contralateral side of the lesion will occur cortical inhibition. The excitation process can induce synaptic plasticity in the infarct area and the inhibitory process can reduce healthy brain activity and provide interhemispheric balance that plays a role in stroke functional recovery (Fisicaro et al., 2019). In the control group only received standard stroke therapy in the form of drugs and medical rehabilitation 3 times a week for 2 weeks. week. Previous research conducted by Long et al (2018) used 3 treatment groups, the first group consisting of 20 people was the control group, the second group consisted of 21 people from the lower frequency (LF-rTMS) group and the third group consisted of 21 people from the group. combination of high frequency (HF-rTMS) 10 Hz with LF-rTMS (1 Hz). In this study, an increase in upper extremity motor function was found using the Fugl-Meyer Assessment (FMA) after being given a combination of low and high frequencies for 2 weeks when compared to other groups. In the control group, there was an insignificant improvement in motor function on examination 15 days after the onset but the results changed to be significant after the follow-up 3 months later (Long et al., 2018). These results are different from the results of our study where there were significant motor changes in the first 2 weeks either in the control and treatment groups where the motoric increase in the treatment group was greater than in the control group. Our results are supported by the study conducted by Du Juan et al, they divided into 3 groups where the group received high-frequency rTMS (10 Hz) intervention on the ipsilateral lesion, low-frequency rTMS (1 Hz) on the contralateral lesion, and the control group had there was a significant difference in the improvement of motor function using FMA after 2 weeks of therapy, but when compared between the treatment group compared to the control group there was a significant difference where the improvement in the treatment group was better than the control group (Du et al. 2019). Similar results were also obtained in a study conducted by Bintang, A.K et al who got the results that there were significant differences in the improvement of motor function using the Stroke Rehabilitation Assessment of Movement (STREAM) in both treatment and control patients, the treatment group in this study received a combination of high frequency and low frequency rTMS while in the control group only received standard stroke therapy (Bintang et al., 2020).

Motor improvement in patients with central nervous system injuries may occur due to the spontaneous healing process. This depends on the remaining activity of the neurons in the penumbra area (the area around the lesion). There are three mechanisms that the brain uses to promote spontaneous recovery after a stroke. The three are reperfusion, edema management, and diaschisis reversal. Reperfusion refers to restoring blood flow to the damaged area. The brain can achieve this in a number of ways, one of which is by increasing blood pressure. For this reason, the researchers recommend caution when trying to lower blood pressure in stroke patients. While very high blood pressure can be dangerous, lowering it too low can hinder spontaneous recovery. Management of edema, decreased oxygen in the brain causes increased swelling (edema), which blocks the blood supply and causes further damage. Therefore, a major part of spontaneous recovery involves reducing edema. This can occur naturally but sometimes requires medication or oxygen therapy. Once the swelling is reduced, blood flow can return, and function is usually restored. Diaschisis reversal, also known as neuroshock, refers to suppressed nerve activity due to loss of input from damaged areas of the brain. This will resolve on its own within a few weeks or by improving blood flow and treating edema (Maher, 2020).

Medical rehabilitation also plays a role in the functional recovery process of post-stroke patients. Plasticity in medical rehabilitation depends on experiential exposure through certain training that can activate neural plasticity mechanisms (Maher, 2020). Training that can activate neural plasticity is training that has repetitive, specific, intensity and long-term nature (Kleim & Jones, 2008). Specific training can increase cortical activity in the brain. ipsilesi brain hemispheres (Lage et al., 2015) and training that has the intensity of spaced practice can increase neuronal activity (Gerbier & Toppino, 2015). The duration of therapy and repeated exercises also affect plasticity, the longer and more frequent the therapy, the better the functional improvement (Thomas et al., 2017; Kwakkel, 2009). With the spontaneous healing process and a successful rehabilitation process. well then in patients who only get drug therapy and physiotherapy can also experience improvements in motor function as we get in the control group of our study.

In stroke patients, EEG recordings were obtained in the form of an increase in slow waves, namely delta and theta. The absolute power of this delta wave is related to the infarct volume. An increase in absolute power in the slow wave frequency band (delta and theta) and a decrease in absolute power in the fast wave frequency band (alpha and beta) are seen in people with decreased brain metabolism such as in stroke (Jordan, 2004). In previous studies, the mean value of DTABR scores in normal people is <1 (Finnigan & Putten, 2013), this is in accordance with our study where the initial DTABR mean value >1 on the six EEG electrodes (Cz, C3, C4, Pz, P3 and P4) and the total DTABR in the control and treatment groups.

In this study we assessed the absolute ratio of delta+theta/alpha+beta wave power (DTABR) at the C3, C4, Cz, P3, P4, Pz and total DTABR electrodes. The reason for taking it at this location is because C3, Cz and C4 are responsible for the motor function of the body. In addition, electrodes located at parietal locations, such as P3, Pz and P4, can also be used to classify motor movement signals as they relate to cognitive processes in the brain (Yahya et al., 2019). Total DTABR represents the overall strength of both slow and fast brain waves on the 19 attached EEG electrodes.

Administration of high-frequency (10 Hz) rTMS stimulation in patients with unilateral lesions can also reduce delta activity on the side of the lesion which may play a role in clinical improvement (Zhong et al., 2021). Administration of rTMS with a frequency of 1 Hz in the motor cortex, increases the absolute power of delta waves in normal subjects (Qiu et al., 2019). Administration of rTMS with a frequency of 10 Hz at point Cz got an absolute decrease in delta wave power on the ipsilateral lesion (Zhong et al., 2021). Based on this we gave 10 Hz stimulation on the ipsilateral lesion and 1 Hz on the contralateral lesion. effect in lowering the value of DTABR. In our results, there was a significant decrease in DTABR consisting of Cz, C3, C4, Pz, P3, P4 and total DTABR in the treatment group with $p < 0.05$.

In the control group there was a significant decrease in DTABR scores with $p < 0.05$ on the Pz and P4 EEG electrodes. The decrease in DTABR in the control group may occur because the control group also experienced a significant improvement in motor function which was assessed after 2 weeks. This can happen because there is a relationship between improved motor function and changes in brain waves shown in previous studies, including

an increase in cortical activation marked by an increase in alpha wave activity in the treatment group receiving Constraint-induced Movement Therapy (CIMT) compared to the control group (Ahmed et al., 2018). This explanation agrees with Carrion et al, who carried out the medical rehabilitation process on 21 patients and found that delta and alpha waves were signs of the recovery process; the higher the alpha power, the better the patient's recovery outcome. They also stated that the relative power of alpha waves has a tendency to increase with increasing motor performance and activities of daily living (Leon et al., 2009). Ingemanson et al 2019, conducted a study on the effect of robotic-assisted medical rehabilitation on 30 chronic stroke patients with upper extremity motor disorders, it was found in 8 out of 9 patients who did not improve had somatosensory disturbances (Ingemanson et al., 2019). Motor improvement depends on the extent of the injury to the sensory system, cortical sensorimotor connectivity and good proprioception. The fewer disturbances in the sensory and proprioceptive systems will give better motor improvement results, this happens because in the medical rehabilitation process, the part of the brain that is stimulated first is the sensory cortex (gyrus post centralis) which is represented by EEG electrodes Pz, P3 and the new P4 will stimulate the motor area (gyrus precentralis). Based on this, a significant decrease in DTABR in the control group can occur in the Pz and P4 areas because these areas are sensory areas plus none of our study samples had proprioceptive disturbances.

Here is a relationship between changes in DTABR and improvements in motor function using the FMA score after the Spearman's test. The relationship is positive, namely the higher the decrease in DTABR the better the motor function as assessed using the FMA. DTABR has a unidirectional relationship with motor clinical outcomes assessed using the modified Ranking Score (mRS) where the lower the DTABR the lower the mRS (Bentes et al., 2018). High delta wave activity is also associated with poor outcome and is associated with loss of consciousness (Leon et al., 2008).

The limitation of this study is the EEG recording process, because at the time of recording the patient was awake, we could not control his mood. An agitated patient can affect the EEG recording by making it predominant for fast waves.

4. Conclusion

Repetitive Transcranial Magnetic Stimulation (rTMS) is effective in improving motor function in ischemic stroke patients. rTMS was also effective in reducing DTABR at the Cz, C3, C4, Pz and DTABR total EEG electrodes. The decrease in DTABR is associated with improvement in motor function, where the higher the decrease in DTABR, the better the motor function.

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ABBREVIATIONS

Abbreviations	Meanings
rTMS	*repetitive Transcranial Magnetic Stimulation*
HF-rTMS	*High Frequency- repetitive Transcranial Magnetic Stimulation*
LF-rTMS	*Low Frequency- repetitive Transcranial Magnetic Stimulation*
DTABR	Rasio (Delta+Teta)/(Alfa+Beta)
FMA	*Fugl Mayer Assesment Test*
FMA-UE	*Fugl Mayer Assesment Test-Upper Extremity*
FMA-LE	*Fugl Mayer Assesment Test-Lower Extremity*
EEG	*Electroencephalogram*
qEEG	*Quantitative Electroencephalogram*

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A Qualitative Study on the Effects of Health Literacy in Population with Hypertension at Blossom Health Care Center, Kabul City, Afghanistan

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Abstract
Hypertension is a chronic disease common in developing countries like Afghanistan, and improving patient awareness of the risk factors and the significance of regular treatment decreases the burden of the disease. In Afghanistan, a higher level of health literacy can help patients with hypertension to know the risk factors, the role of lifestyle management, and the significance of regular treatment for hypertension. Also, a higher level of health literacy can provide venues for the patient to comprehend the provided information and actively participate in the care. Alternatively, patients with lower health literacy might need to appropriately understand the information related to diet, treatment, and provider communication during the management of hypertension. A lack of understanding of hypertension-related treatment suggestions might lead to poor compliance with hypertension medication. This qualitative study aimed to assess the health literacy level among patients seeking care for hypertension at Blossom Health Care Center in Kabul, Afghanistan. A total of 198 patients who had hypertension participated in the study, and patients were interviewed using a Likert scale for responses generated by a focus group of 10 Afghan doctors practicing in Kabul, Afghanistan. We found that 68.7% of patients with hypertension scored Strongly Disagree to having adequate hypertension knowledge. Moreover, around 37.3% of participants indicated Always visiting a doctor for this condition, and 38.4 indicated Always taking their medication. Studies have shown that lower health literacy in patients with hypertension might negatively impact their health outcomes. Therefore, increasing awareness and knowledge of hypertension related-treatment among people with hypertension might improve their overall health and well-being.

Keywords: Hypertension, Health Literacy, Developing Countries, Compliance, Communication

1. Background

Studies on noncommunicable diseases such as hypertension are limited in Afghanistan. One of the significant reasons that make it challenging to estimate the prevalence of hypertension in Afghanistan is the lack of adequate resources in the health system to provide high-quality data (Saeed, 2017). According to the World Health

Organization's (2018) hypertension fact sheet, around 29.5% (5.3 million) of Afghan adults have hypertension. Moreover, the fact sheet indicated that of the 5.3 million patients with hypertension, 4.2 million patients had poor control of their high blood pressure. According to Mills et al. (2020), in addition to the increase in the prevalence of hypertension in low- and middle-income countries such as Afghanistan, the proportion of hypertension awareness is also low, and uncontrolled urbanization, which can decrease physical activity and increase unhealthy diets, is believed to be the leading factor of hypertension (Ibrahim & Damasceno, 2012). In addition, low literacy rates and poor health care significantly impact awareness of available treatments, treatment compliance, and access to care in Afghanistan (Khan et al., 2022).

1.1. Health Literacy

Health literacy emerged in the health system in the 1970s (Simonds, 1974). Health literacy does not have a universal definition. Molloy-Weir et al. (2016) indicated that there are around 250 definitions of health literacy in the medical literature. Health literacy is a person's ability to understand, locate, and process health information to make reasonable health-related decisions (National Institutes of Health, 2021). Also, health literacy entails three items 1) familiarity with healthcare and health system-related, 2) processing health information, and 3) communication with doctors (Liu et al., 2020).

In the last two decades, health literacy has been a crucial concept in the health system because it can improve population and public health and stabilizes health system finance. (Liu et al., 2020). Just as healthcare services are increasing, people need to know how to stay healthy and effectively use healthcare services to decrease the strain of expenses (McQueen et al., 2007). People with poor health literacy might need to adequately understand the nature of a disease, which can raise the chances of poor compliance with prescribed drugs and inappropriate use of services in health settings (Logan, 2017; Sheridan et al., 2011). Many countries are grappling with the burden of non-communicable diseases. Pleasant et al. (2015) suggested that improving health literacy is an excellent approach to decreasing the burden of different chronic conditions.

Also, health literacy can enhance people's autonomy and participation in care, improving their health outcomes (Samerski, 2019). The relationship between health literacy and medical decisions is assessed, and it is observed that people with lower health literacy participate less in their care (Smith et al., 2014). Moreover, Nutbeam (2008) highlighted that health literacy is a personal asset that can enhance patient skills to make healthcare decisions independently.

Older, disabled, uneducated, and poor people are disproportionally affected by lower levels of health literacy (Kutner et al., 2006). People with suboptimal levels of health literacy are prone to developing chronic diseases (Cavanaugh et al., 2008) because they are less likely to use preventive care and participate in their care (Schillinger, 2021).

1.2. Health Literacy in Afghanistan

The literacy level in Afghanistan was 43% for men and women combined in 2019 (United et al. Organization,2020). Furthermore, according to Harsch et al. (2021), research on health literacy is limited in Afghanistan. In a survey of women from four Hazarajat districts in Shuhada Hospital in Ghazni, Afghanistan, they found that 51.6% of women had a lower level of health literacy and 22.7% had an optimal level of health literacy (Harsch et al., 2021). In the regression analysis, they noticed that education was the most critical predictor of health literacy. Also, they noticed that having access to the internet, technology, educated family members, and electricity are the other common predictor after education for health literacy among women (Harsch et al., 2021).

Furthermore, Harsch et al. (2020) found that women with higher levels of health literacy seek healthcare services more than women with lower levels of health literacy. Levy and Janke (2015) found that patients with lower levels of health literacy are more likely to delay their care. Also, Harsch et al. (2021) found that women with higher levels of health literacy sought care from clinicians, and their level of health literacy was significantly associated

with breastfeeding (p=0.001), health-seeking behavior from a professional (p<0.001), and giving birth in a healthcare facility (p<0.001).

Hickey et al. (2019) suggested that the potential elements of a lower level of health literacy are lower access to education, inconsistent access to healthcare services, and a lack of awareness campaigns. According to the World Bank (2023), around 37% of the total population of Afghanistan was literate in 2021. Rostamzadeh et al. (2022), in a cross-sectional study conducted at Barchi National Hospital in Kabul, Afghanistan, on 200 participants, indicated that the level of health literacy among pregnant women was low, and one of the participants' health literacy-associated factors was education level. By investigating the effects and factors of low health literacy, it is also necessary to identify one specific health condition and its effects, if any, on treatment outcomes in developing countries that may be influenced by low health literacy levels.

1.3. Hypertension: Incidence and Influences

According to the Noncommunicable Disease Risk Factor Collaboration (2017), the number of people with hypertension has increased from 594 million to 1.13 billion over the last four decades. The treatment of hypertension accounts for 10% of healthcare expenses globally (Gaziono et al., 2009). This vast increase in the prevalence of hypertension globally can be attributed to its rapid growth in low- and middle-income countries. Population growth variation in low, middle, and higher-income countries can influence the increase in cases. For example, in 2010, nearly 349 million people lived in developed countries, whereas 1.04 billion people lived in low- and middle-income countries (Lindenfield & Jessup, 2017). According to the Global Health Observatory (2022), 41 million lose their life to noncommunicable diseases, including hypertension, annually, and 85% of those deaths happen in low- and middle-income countries.

Other factors that influence the increase in cases of hypertension in developing countries are an unhealthy diet (i.e., excessive salt consumption or poor access to fresh fruits and vegetables), obesity, lack of physical activity, and tobacco and alcohol use (O'Donnell et al., 2020; Popkin et al., 2020; Zhao et al., 2011). Other emerging risk factors are air pollution, uncontrolled urbanization, and reduction in green space (Schutte et al., 2021). In a provincial cross-sectional study in Kabul City, Afghanistan, Saeed (2017) found that significant predictors of hypertension were general obesity, central obesity, tobacco use, limited physical activity, and inadequate consumption of fruits.

1.4. Hypertension and Health Literacy

Even though the level of health literacy is different between countries, surveys from developing countries reveal that a significant proportion of the population has a suboptimal level of health literacy (Duong et al., 2020). Multiple investigations are available on the role of health literacy in recognizing and treating hypertension (Magnani et al., 2018). McNaughton et al. (2014) highlighted this relationship in an observational cross-sectional study of patients enrolled in a randomized controlled trial. The results indicated that patients with lower levels of health literacy had a 1.8 to 2.7 greater risk of not obtaining optimal blood pressure and lower adherence to refilling their medication (McNaughton et al., 2014). Patients with lower levels of health literacy are prone to misunderstand and misuse medications prescribed for the treatment of hypertension. Magnani et al. (2018) indicated that patient-centered, health literacy-specific education could improve hypertension medication compliance in patient populations with lower levels of health literacy. Patient-centered educational interventions can also reduce patient misunderstanding of the provider's instructions (Magnani et al., 2018).

For example, a 2-Arm multisite patient randomized pragmatic trial by Wolf et al. (2016) used patient-centered drug labeling to improve diabetes and hypertension medication compliance in the study participants. Patient-centered label strategies that integrated evidence-based practices such as larger font size, white space, and conveying instruction via Medication Universal Schedule (morning, noon, evening, and bedtime) appeared to affect patient outcomes positively. A simple modification to medication labeling with minimal financial cost improved medication compliance. The result of Wolf et al. (2016) indicated that the intervention improved medication compliance among participants with lower levels of health literacy 4-fold. Another small study (n=68)

by Yeung et al. (2017) found that digital and physical aids, such as flashcards and short videos, helped patients comply with their medication schedules. Implementing individualized educational strategies in a simplified regimen and other multilevel strategies helped improve blood pressure control in patients with low health literacy levels (Magnani et al., 2018).

1.5. Health Literacy Patient-centered Education and Medication Compliance

A patient population prescribed multiple medications makes these patients susceptible to self-administration medication errors. This risk is higher among people with lower levels of health literacy (Davis et al., 2006). In a systematic review, Berkman et al. (2011) highlighted that low health literacy can lead to suboptimal health outcomes. A possible causal correlation between low health literacy and poor health outcomes is attributed to poor medication reconciliation, knowledge, and medication self-management (Mackey et al., 2016; Patzer et al., 2016; Persell et al., 2007).

Mackey et al. (2016) indicated that a patient population with a lower level of health literacy might not appropriately communicate the list of medications they regularly take in situations where the provider needs to reconcile the active list of medications. According to the World Health Organization (2017), health literacy enables the patient population to actively engage in medical decisions, and they consider health literacy a crucial health determinant. Additionally, higher health literacy might enhance healthy behavior; Bruthan et al. (2016) highlighted that low health literacy could lead to a higher prevalence of cardiovascular risk factors in patients with cardiovascular disease due to lower health-related knowledge.

1.6. Issues with Lack of Training for Healthcare Professionals

Healthcare providers are well-trusted sources for conveying health information to many community members. Building trust can improve cooperation between healthcare clinicians and the patient population, enhancing the success of the treatment interventions (Castro et al., 2016). Moreover, Castro et al. (2016) highlighted that interactive communication between providers and the patient population during healthcare delivery could improve treatment protocol efficiency and reduce costs. In the health system, health literacy is vital to interactive and effective communication (Wu et al., 2016).

Unfortunately, many healthcare providers are either unaware or untrained in using health literacy strategies for proper patient education in managing chronic disease.

In a cross-sectional analytic study, Mor-Anavy et al. (2021) found that one-third of the participants (providers and administrators) needed to learn that a lower level of health literacy could contribute to unnecessary healthcare services. Furthermore, they noticed a significant association ($p<0.05$) between clinicians' awareness of health literacy methods and strategies and their attitudes to promoting health literacy using various approaches to communicate effectively with a patient with a lower level of health literacy. Improving health literacy among the patient population with hypertension can be problematic if we do not improve the skills of the providers and healthcare professionals related to health literacy intervention and initiatives (Parker & Ratzan, 2010).

1.7. Possible Interventions and Solutions

1.7.1. Provider Training

The Agency for Healthcare Research and Quality Health Literacy Universal Toolkit can help healthcare professionals simplify health care and improve patient understanding of health information. Using this Toolkit can help educate providers on methods to assist patients with various levels of health literacy to increase compliance with treatment recommendations. Health literacy universal precautions steps aim to simplify communication to improve patients' comprehension, decrease the risk of miscommunication, make health system navigation more straightforward, and support patients in improving their health (Brega et al., 2015). (See Table 1).

Health literacy's relationship to blood pressure control is assessed in multiple studies. Pandit et al. (2009) found that multivariable analysis associated lower health literacy with uncontrolled hypertension. Hall et al. (2016) highlighted that a higher level of health literacy is associated with optimal blood pressure using hierarchal and logistic regression. Health literacy dimensions such as access to information and decision-making were critical elements of a healthy lifestyle in improving blood pressure in a cross-sectional study in Iran (Gaffari-Fam et al., 2020).

Table 1: Health Literacy Universal Toolkit

Tool	Title
1	Build a team
2	Make a roadmap for health literacy improvement
3	Expand the level of health literacy
4	Use plain language
5	Apply the tell, ask, listen, and understand? method
6	Follow up the patients
7	Improve access to communication tools
8	Reconcile patient medications
9	Address language barriers appropriately
10	Respect patients traditional and cultural beliefs
11	Use the material that are easy to comprehend
12	Apply educational materials appropriately
13	Accept patient with nice attitude
14	Listen to the questions and motivate patients to ask questions
15	Create action plan
16	Assist patient in remember medication time and use
17	Listen to the patients concerns and recommendations
18	Guide patients to supportive resources
19	Guide patients to medical resources
20	Introduce patients to health literacy programs
21	Make care transition smooth

Source: Brega, A. G., Barnard, J., Mabachi, N. M., Weiss, B. D., DeWalt, D. A., Brach, C., Cifuentes, M., Albright, K., & West, D. R. (2015). AHRQ health literacy universal precautions toolkit. https://www.ahrq.gov/sites/default/files/publications/files/healthlittoolkit2_4.pdf.

1.7.2. Lifestyle Modification

Preventing chronic diseases like cardiovascular disease depends on self-care competencies (Riegel et al., 2009). According to Riegel et al. (2004), self-care is a naturalistic decision-making process that the patient population uses to choose behaviors to stabilize physiological functions, and health literacy entails some of the critical skills that can empower self-care components such as understanding health information and comprehension of healthcare professional messages (Aaby et al., 2017). A large population-based study, Aaby et al. (2017) found a remarkable association between health literacy and self-care, such as physical activity, healthy diet, and comprehension of medical information in a patient population with self-reported cardiovascular disease.

Lifestyle modifications such as physical exercise, a healthy diet, and bodyweight management are essential to controlling hypertension (Te Riet et al., 2015). Self-management is a vital step in controlling hypertension. Du et al. (2018) suggested that the patient population needs adequate health literacy to comprehend the educational material on hypertension and apply the learned concepts in their daily routine.

1.7.3. Communication with Providers

Multilevel and multidisciplinary strategies prioritizing communication and patient empowerment can improve medication adherence. In the case of hypertension management, interventions that support patients at the community level can have a positive impact through local outreach, providing health literacy level appropriate education, and offering community-based monitoring of blood pressure levels (DeWalt et al., 2010; Náfrádi et al., 2016).

Castro et al. (2016) highlighted that patient care which entails interactive communication and promotes self-management and patient involvement in the care could make healthcare services effective and efficient. Health literacy is crucial to effective communication in healthcare service delivery (Wu et al., 2016). Study results indicated that people with low health literacy encounter challenges in grappling with chronic health conditions and exploring the health system (Heijmans et al., 2015; Miller, 2016). For example, a lack of comprehension of providers' instruction in oral, written, and digital forms can lead to difficulties in communication with providers and affect adherence to new information (Rowlands et al., 2015). Therefore, it is crucial for providers to understand how to create health literacy-appropriate educational materials to educate patients at all levels, thus improving patient-centered communication. Coleman (2013) suggested that ineffective communication between providers and patient populations can lead to miscommunication and suboptimal compliance with treatment recommendations.

2. Study Design

The study used a qualitative design using a survey from a convenience sample in **Blossom Health Care Center**, Kabul City, Afghanistan. The survey questionnaire was created based on the providers' concerns about poor compliance with hypertension medication, suboptimal follow-ups, and misunderstanding of the uses of hypertension medication. Therefore, a focused group of 10 doctors with experience in Adult Internal medicine working in Kabul City and with experience treating hypertension patients Kabul City residents created a survey questionnaire to assess the level of health literacy of patients with hypertension for educational and awareness purposes.

2.1. Methods

From February 2023 to May 2023, 198 patients were interviewed in person. At the end of the patient's visit, the provider asked the patient if they would like to participate in the survey on health literacy in patients with hypertension. For data collection and analysis, surveys were deidentified, and patient information was not collected to maintain confidentiality. The study's objective was explained to the patient that it was for educational purposes. After the patient's consent, the participant's demographics, care continuation, and regular use of their medication were asked verbally based on the patient's preference in Pashto and Dari at **Blossom Health Care Center** in Kabul City, Afghanistan. Formal approval from the **Blossom Health Care Center** in Kabul City for this Exempt review was obtained for the anonymous collection of survey data and responses to the survey.
Question 1: Do you think you have adequate knowledge of hypertension?
Question 2: Do you regularly follow up with a provider for hypertension?
Question 3: Do you regularly take your hypertension medication prescribed by your provider?
Question 4: Do you know how long you have had hypertension?

2.2. Inclusion and Exclusion Criteria

We included patients above 18 years old and excluded patients who did not have hypertension and were not residents of Kabul City, Afghanistan.

3. Results

A total of 198 patients with hypertension were surveyed. About 30.3% of participants were male, and 69.7% were female. Participants' educational backgrounds include high school graduates (13.6 %), bachelor's (15.6%), master's (0.5%), doctorate (2.5%), and illiterate (67.8%) (See table 2).

Table 2: Survey Participants Demographics

Variable	**Population (n=198)**	**Percentage**
Gender	Men (n= 60)	30.3
	Women (n= 138)	69.7
Educational Backgrounds	High School Graduate (n= 27)	13.6
	Bachelor's degree (n=31)	15.6
	Master's degree (n= 1)	0.5
	Doctorate (n= 5)	2.5
	Illiterate (n= 134)	67.8
Age	>18 years old (n= 198)	100

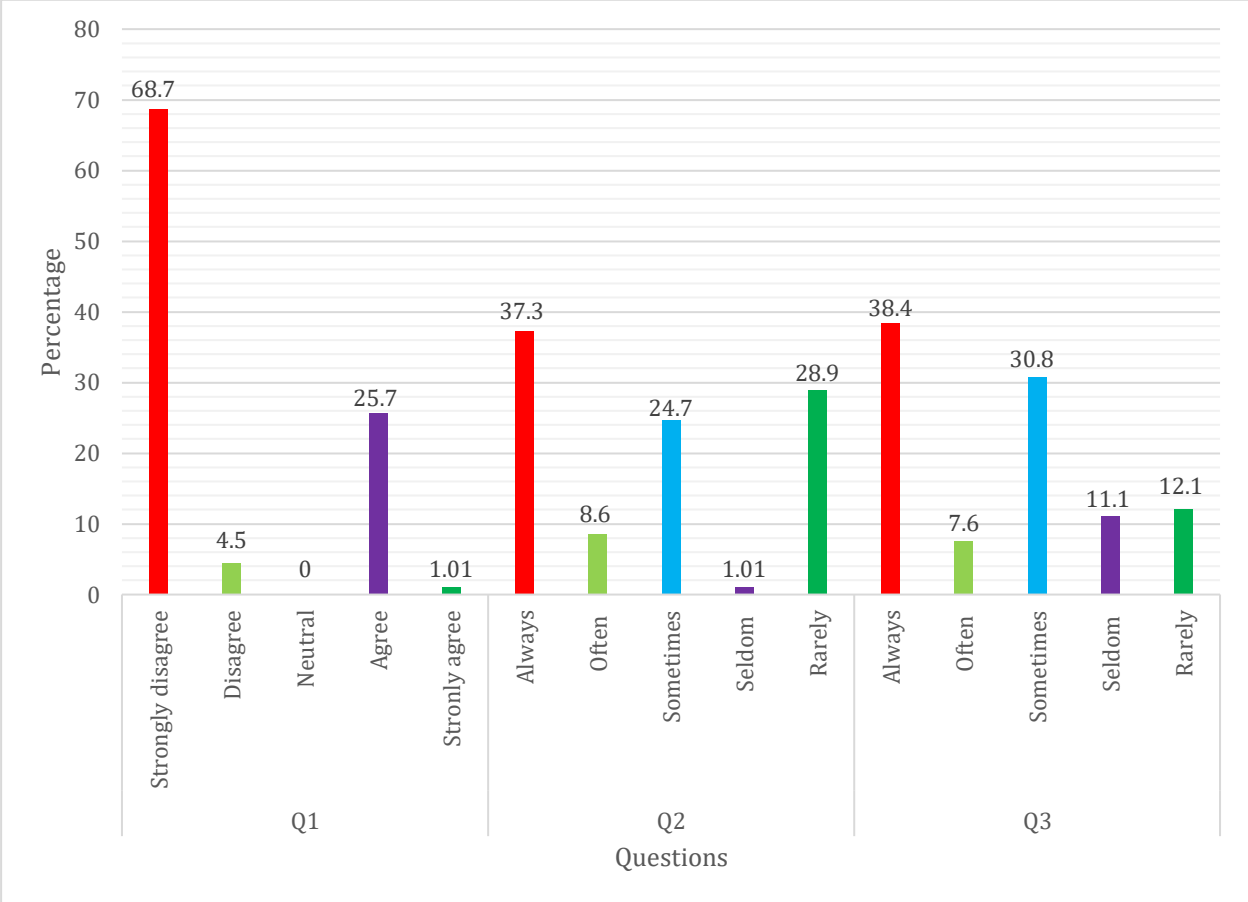

Figure 3: Responses to Question 1, 2, and 3

Likert scale scoring criteria are used to score participants' responses to the questions in the survey. In the sample, 68.7% of participants Strongly Disagree, and 25.7% Agree with having adequate hypertension knowledge. For doctor's visits, around 37.3% always visit a doctor, 8.6% often, 24.7% sometimes, 1.01% seldom, and 28.9% rarely visit a doctor for hypertension. Furthermore, around 38.8% of participants indicate that they always take their medication for hypertension, and 7.6% often, 30.8% sometimes, 1.01% seldom, and 28.7 rarely. (See figure 3)

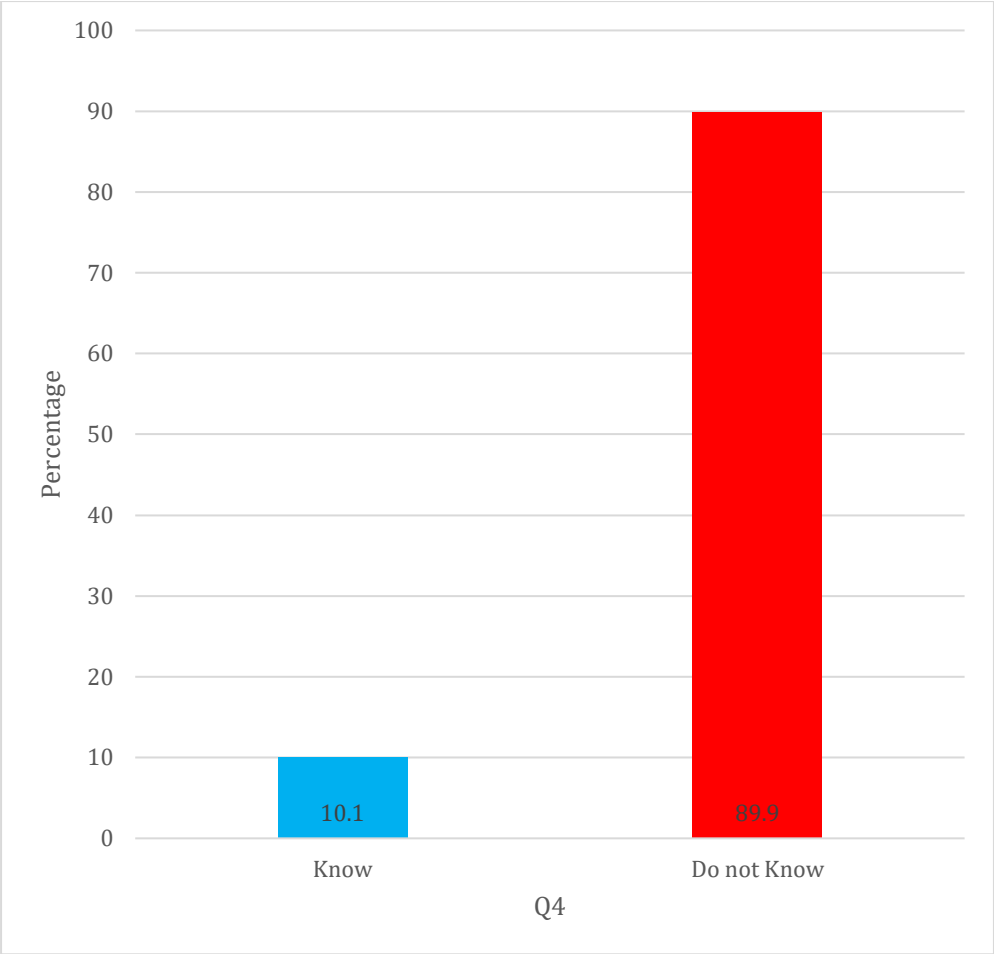

Figure 4: Responses to Question 4

Regarding how long the participants have a history of hypertension, around 10.1% know how long they have a history of hypertension, and around 89.9% do not know how long they have a history of hypertension. (See Figure 4)

4. Discussion

According to the World Bank (2023), around 37% of the total population of Afghanistan was literate in 2021, and research on health literacy is limited in Afghanistan (Harsch et al., 2021). We found that around 68.8% of participants strongly disagreed, and 25.7% agreed to have adequate hypertension knowledge. Harsch et al. (2021) found that 51.6% of women had a lower level of health literacy, and 22.7% had an optimal level of health literacy in Ghazni, Afghanistan. Also, Rostamzadeh et al. (2022), in a cross-sectional study conducted at Barchi National Hospital in Kabul, Afghanistan, indicated that the level of health literacy among pregnant women was low, and one of the health literacy-associated factors was education level.

Multiple study results highlighted that low health literacy and poor health outcomes are attributed to poor medication reconciliation, knowledge, and self-management (Mackey et al., 2016; Patzer et al., 2016; Persell et al., 2007). We found that 38.5% of participants always and 30.8% sometimes take their hypertension medication. Moreover, Magnani et al. (2018) indicated that patient-centered, health literacy-specific education could improve hypertension medication compliance in patients with lower levels of health literacy. Patient-centered educational interventions can also reduce patient misunderstanding of the provider's instructions (Magnani et al., 2018).

5. Limitations

We cannot generalize the results of this study due to the nature of the study, which is qualitative, and the data is collected through face-to-face interviews with potential interviewer biases. Also, Blossom Hospital is a private hospital. People with lower income might not be able to afford their care there, and the sample might not be representative of patients with lower income.

6. Conclusion

Hypertension is a non-communicable disease that needs regular management. A patient's appropriate level of health literacy can be essential in comprehending the information regarding healthy behavior, participating in care, and maintaining compliance with medication. In Afghanistan, low literacy and health literacy levels can negatively impact patient outcomes and overall well-being. Programs to increase patients' awareness and hypertension knowledge can decrease the burden of early complications from hypertension, positively impacting the health system in general. In addition, provider training on using health literacy-appropriate concepts and materials may also be essential in improving the quality of care for patients with hypertension in developing countries like Afghanistan.

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Evaluating the Strength of Evidence on the Effectiveness of Accommodative Support Lens on Computer Vision Syndrome

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Abstract
Computer vision syndrome is a disease that has emerged with the advent of the computer and digital age. It is most associated with long-hour users of digital screen devices. Its symptoms are ocular and extraocular and may include blur or double vision, and other visual discomforts such as redness, irritation, dry eye, watery eye, headache, neck and shoulder pains, back aches and tendonitis. Several studies have reported a prevalence rate of between 10-90%. Depending on a number of factors, different treatment approaches have been adopted by physicians for primary and secondary care. These approaches include optimization of ergonomics, progressive addition of lenses, use of nutritional supplements, and artificial tears. The validity of the efficacy of these approaches has continued to generate debates among public health stakeholders due to limited evidence. This article discusses the strength of evidence of the use of accommodative support lenses in alleviating the symptoms of computer vision syndrome, with a special focus on the work of Seguí-Crespo et al., 2022.

Keywords: Computer Vision Syndrome, Accommodative Lenses, Occular, Extraoccular, Digital Screen, Ergonomics

1. Introduction

1.1 Computer vision syndrome

Computer vision syndrome (CVS) defines a set of eye and vision-related symptoms found in ardent users of computer screens and other digital video display terminals (Singh *et al.,* 2022). Symptoms of CVS are associated with either ocular surface resulting from dryness, burning, tearing, irritation, or with ocular interior aberrations from refractive errors, and accommodative or binocular vision errors (Seguí-Crespo *et al.,* 2022). Common symptoms of CVS include blurred vision, double vision, visual discomfort, dry eye disease (DED), redness, irritation, and watery eye. Extraocular symptoms of CVS include headaches, neck and shoulder pains, back aches, and thumb or wrist tendonitis (Alamri *et al.,* 2022). About 40% and 80% of CVS prevalence have been reported in adults and teenagers, respectively. Studies have indicated population prevalence ranging from 10% to 90% in different communities (Iqbal *et al.,* 2021).

The majority of the symptoms of CVS are temporary, recurrent, prone to progression, and may not resolve at the close of working hours (Singh *et al.,* 2022). The biological mechanisms of some of these symptoms are not well defined, and may also be dependent on other factors like ergonomic designs of the workstations. Some CVS symptoms are worsened by age and length of use of the device. Early studies indicate risk factors for CVS as the duration of computer device use (over 2 hours per day), glare and reflections on the device screen from surrounding lighting, humidity lower than 40%, and poor ergonomics (Singh *et al.,* 2022). The multifactorial nature of CVS symptoms makes studies in the field prone to 'effect modification' or 'interaction' bias, which has to be considered and attenuated in study designs (LaMorte and Sullivan, 2016). Many researchers have postulated that the blue light (short-wavelength visible light) from the computer screen causes CVS eye strain and may worsen accommodation. This has however remained contentious due to the lack of supporting evidence, the absence of convincing biological mechanisms, and the low level of emission of blue light in modern digital screens (Singh *et al.,* 2021).

1.2 Approaches to CVS Diagnosis and Treatment

In primary vision care, a range of symptom-targeted case-definition questions are used to diagnose CVS in patients who use computers regularly. The questions also determine the frequency and intensity of symptoms. Laboratory confirmatory tests may be required for confirmation of some ocular abnormalities. The CVS diagnostic questionnaires have been used by many researchers across the world to clinically identify CVS (Singh *et al.,* 2022). The questionnaire was standardized and validated as CVS-Q© by Segui *et al.* (2015). Clinical management of CVS incorporates several treatment approaches ranging from ergonomics optimization; applying the 20-20-20 rule (viewing an object 20 feet away for 20 seconds every 20 minutes) (Coles-Brennan *et al.,* 2019); progressive addition of spectacle lenses (Kee *et al.,* 2018) and blue light blocking spectacle lenses (Lin *et al.,* 2017); use of oral antioxidant and nutritional supplements like oral omega-3 fatty acid supplements and bilberry extracts (Bhargava *et al.,* 2013, 2016; Ozawa *et al.,* 2015); use of artificial tears (Blehm *et al.,* 2005); and traditional medicines such as *Triphala arka* (a polyherbal ayurvedic medicine) and *Saptamrita lauha* (a compound herbomineral ayurvedic formulation) (Gangamma *et al.,* 2010). Some of these treatment approaches are advertised directly to patients despite limited evidence of their efficacy. For instance, progressive addition of lenses is promoted for reduced CVS symptoms in pre-presbyopic adults (Kee *et al.,* 2018), and in non-presbyopes (Koh *et al.,* 2020); blue light-blocking spectacle lenses are promoted to lessen symptoms of eye strain from digital-screens (Essilor, 2022 and Zeiss, 2021, as cited in Singh *et al.,* 2022); oral omega-3 fatty acids nutritional supplement is believed to lessen dry eye symptoms (Bhargava *et al.,* 2013, 2016); and artificial tears are promoted as lubricants for the ocular surface to lessen CVS symptoms (Blehm *et al.,* 2005; Coles-Brennan *et al.,* 2019).

Contemporary preventive lifestyle for CVS accommodative problem recommends the use of newer designs of spectacle lenses with progressive-power options for pre-presbyopic individuals (Segui-Crespo *et al.,* 2022). Such spectacle designs are equipped with 'accommodative support' (AS) to reduce accommodative demands during extended use of digital screens (Wahlberg *et al.,* 2010). Despite the perceived benefits, there has been no definite consensus on the efficacy of low-plus lenses on CVS due to a lack of reliable, valid, and conclusive data from randomized controlled trials (RCTs) (Brautaset *et al.,* 2008; Wahlberg *et al.,* 2010; Yammouni and Evans, 2020). Another limitation in previous studies was the study duration which was considered short to expose the longer-term effect of accommodative spectacles. It is against these considerations that a more recent epidemiological study by Segui-Crespo *et al.* (2022) to determine if accommodative support lenses improve CVS symptoms, is being discussed for public health relevance.

2. Discussion

2.1 Strength of Evidence on Accommodative Support Lenses

The prospective double-masked randomized controlled trial by Segui-Crespo *et al.* (2022) explored the effect of accommodative support lenses on CVS symptoms, its perceived benefit from the binocular vision and accommodative functions, and the consequence on binocular and accommodative functions if used for 6 months. The study which was based on CVS-Q© score indicated that accommodative support lenses did not produce significant CVS symptom improvement in pre-presbyopic adults. It also indicated that there was 'no adverse effect

on optometric function (including accommodation)' associated with wearing accommodative support lenses. While these outcome interpretations may be of reasonable relevance in contemporary public health, it is important to critically evaluate the study for epidemiological weakness or limitations for planning public health intervention or improving future studies.

The risk factors for CVS are multifactorial and may range from individual demography and genetic makeup to environmental factors (humidity) and workstation ergonomics. As a result, non-RCTs and RCTs studies face bias from participant selection (random), data collection and confounding, which contribute to weakness and limitation of study evidence, and downgrade its reliability and validity, as well as limit outcome interpretations and applicability (Matsui and Keet, 2017; Pinchbeck and Archer, 2020). For instance, the effect of confounding such as low-level uncorrected astigmatism (0.50–1.00 DC), and other underlying vergence problem may be implicated in CVS accommodative symptoms and may invalidate an otherwise good study (Seguí-Crespo *et al.,* 2022).

The study under examination was appropriately conceptualized to understudy the long-term advantage of the use of accommodative support (AS) lenses over single vision (SV) lenses in improving CVS symptoms adduced to accommodative demands using CVS-Q©. The research questions were appropriately based on hypotheses and scope of study to adequately address the aim. All participants attained a minimum CVS-Q© score of 6 to confirm CVS at baseline before being randomized in double-masked randomization. Perhaps a higher score of about 12 (closer to the mode of the selected participants) could have been more definitive of a more homogenous population for participant selection. The major weakness in the focus of the study arises from the fact that the definition of CVS and its symptoms as provided in CVS-Q© is multifactorial and may not be reduced by fixing accommodative problems alone. In my view, this was also not adequately addressed in the design and methodology.

The double-blind RCT was adequate to eliminate selection bias after screening selection, however, the inclusion and exclusion criteria were limited in scope. The criteria did not provide for variability in ergonomics, environment humidity and air-pollutant, duration of screen use, user workload and associated psychosocial stress, use of a nutritional supplement, level of physical activity, as well as the socioeconomic status of participants. The study did not indicate whether the presence of other non-CVS health conditions, which could have affected extraocular symptoms (neck, shoulder, and headaches) and baseline health status, were included in the exclusion criteria. Hereditary disposition (astigmatism), age, and gender are risk factors for CVS and accommodative loss (Dirani *et al.,* 2008; Lockhart and Shi, 2010; Sun *et al.,* 1988), and could be sources of confounding. Some studies have shown that accommodative problems become more apparent from above age 30yrs (Sun *et al.,* 1988), but this study recruited participants of age 18-40yrs. These confounding factors were not adequately eliminated.

The study design of double-blind RCT attempted to eliminate selection bias significantly (Matsui and Keet, 2017; Pinchbeck and Archer, 2020). Primary selection bias may still have been carried over from the screening or pre-randomization stage. Such bias may affect mean age, workload, and ergonomics. The attrition rate was low (2.2%), and hence the study did not suffer from attrition bias. In addition to the biases discussed above, self-reporting questionnaires such as CVS-Q© are very subjective and often prone to 'recall bias'. Follow-up studies of this nature where participants were followed up monthly for reminders, and then assessed on the 3rd and 6th month, are also prone to 'differential assessment bias' as the study progress, and/or 'exposure suspicion bias' where there is suspected outcome development by the data collector or the participant. The laboratory confirmatory test at baseline, 3rd, and 6th months may have minimized some of the self-reporting 'information bias'.

The confirmatory data collected were typical for accommodative vision. The analysis of results was adequately performed by comparing AS (treatment group) and SV (control group) using Microsoft Excel (version 2102) and IBM SPSS (version 26) tool. The preference for the AS spectacles by the control group at the end of the study may be an indication of the improvement of CVS by AS lenses. However, it was not adequately studied since it was unmasked and subject to 'reporting bias'.

The authors' conclusion that the AS did not confer any advantage on resolving CVS was appropriate and based on the fact that there was no improvement in CSV-Q© score over 3 to 6 months. The study also found no strong

optometric correlation between the use of accommodative lenses and improved CVS (Segui-Crespo *et al.,* 2022, pg. 92).

2.2 The Implication of the Strength of Evidence

According to the hierarchy of evidence, evidence from the RCT study is rated Level 2, and is more reliable and generalizable than Level 3 and beyond (Krueger, 2022). The double-masked RCT study by Segui-Crespo *et al.* (2022) falls into this category and was appropriate although it contains certain weaknesses from the biases discussed above, which may have downgraded its reliability and validity for public health applications.

As earlier discussed, the study did not show adequate provision for the elimination of information bias and confounding from other risk factors of CVS. It also did not attempt to explain limitations due to 'effect modification' or 'interaction' from differences in the socioeconomic status of the participants, and other CVS multifactorial variables like humidity, air-irritants, ergonomics, heredity, nutritional supplements, gender, age, and workload, on participants' accommodative response and CVS-Q©. Statistical interactions due to interloping third variable(s) were not adequately discussed (LaMorte and Sullivan, 2016). The existence of these biases from uncontrolled confounding factors provides a basis to question the reliability and internal/external validity of the study. The statistical power for sample size determination was not stated. The sample size appears small hence the study may not be reliable and internally valid.

There will be bias in the estimate or interpretation of outcome variables when confounders are not statistically adjusted for or explained to establish perspectives to the limitation of the study (LaMorte and Sullivan, 2016). This may create divergence among study populations or groups when no real divergence exists, or/and a report of an association when there is truly none. Confounding can also result in under or over-estimation of study outcomes (Public Health Action Support Team, PHAST, 2022). Finally, the study was sponsored by the industry and therefore prone to bias from conflict of interest.

3. Conclusion

Computer vision syndrome is a growing occupational health risk among computer users. Accommodative vision problem is one of the symptoms of CVS. Many researchers have theorized that accommodative problems in CVS could be ameliorated with the use of accommodative support lenses. Earlier studies to investigate the correlation between accommodative support lenses and attenuation of CVS symptoms showed several limitations including a lack of randomized controlled trials and short study duration. The study by Segui-Crespo *et al.* (2022) aimed to investigate the correlation between improved CVS symptoms and the use of accommodative support lenses in a double-masked randomized controlled trial, over a longer period of six months. The study aim, research questions, hypotheses, and design seemed appropriate. The methodology shows loopholes and susceptibility to biases. The sample size statistical power was not stated, and the sample size was small compared to similar CVS studies by Iqbal *et al.* (2021). The conclusion that there was no strong correlation between wearing accommodative support lenses and improvement in CVS symptoms and no adverse effect on optometric function due to the use of accommodative support lenses seemed appropriate. The biases of note in the study include systemic biases such as information bias and confounding bias. These biases suggest that the study may not be reliable and valid, limiting its public health application. Subsequent studies in the field should consider higher sample size and statistical power and attenuation of confounding factors of astigmatism, environment, ergonomics, and workload, amongst others. Despite the foregoing, the no-benefit conclusion of the study will assist public health officials to make more appropriate decisions on CVS interventions and future studies. This will help in the efficient deployment of resources.

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Conflict of Interest

There is no conflict of interest. The author has no specific financial or material interest in developing the manuscript other than to contribute to scientific knowledge on CVS. There was no specific funding from any funder.

Ethical Approval and Consent

The article does not include any primary data from enrolled participants. It does not contain any collection or report of primary biological data or any participants' identifying information. Hence no ethical approval of study was necessary.

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Author Contribution

HOE conceptualized, conduct literature review, and developed the manuscript.

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Alternative Antibiotics Therapy for Drug-resistant Gonorrhea: A Literature Review

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Abstract
Background: The management and control of gonorrhea are hampered by the widespread resistance to the diverse strains of *Neisseria gonorrhea*. Resistance to sulfonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early cephalosporins has emerged rapidly. Purpose: This systematic review aimed to assess what antibiotics can be used as an alternative therapy for gonorrhea infections that are resistant to antibiotics. Methods: The study was conducted using the Web of Science, PubMed, Embase, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines. Risk of Bias for Randomized Trials (RoB2) was utilized to evaluate study quality. Results: This review included 28 articles from randomized controlled trials between 2013 and 2023, distributed across five nations. The studies included 2.380 patients and clinical isolates from men and women diagnosed with gonorrhea infection at various sites. Sample testing by treatment with alternative antibiotics. Discussion: Zoliflodacin, tigecycline, and ertapenem in single or dual therapy with ceftriaxone could be considered as a potential option in treating gonorrhea resistant to antibiotics. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gepotidacin is effective for the Gyr A A92T mutation in gonorrhea infection. Summary: The effectiveness of these antibiotics, zoliflodacin, ceftriaxone, gentamicin, gepotidacin, solithromycin, tigecycline, and ertapenem is considered a solution to gonorrhea resistance. Researchers should study how to provide antibiotics with intervening multidrug efflux pumps to overcome gonococcal antimicrobial resistance.

Keywords: Gonorrhoea, Resistance Antibiotic, Alternative Antibiotics

1. Introduction

The prevalence of bacterial resistance to antibiotics is accountable for a significant number of fatalities annually, reaching hundreds of thousands. One of the most pressing issues pertains to the escalating prevalence of bacteria that have developed resistance against frequently employed antibiotics, particularly those considered the final line of defense. This requires international cooperation. In 2014, the World Health Organization (WHO) acknowledged this occurrence as a significant worldwide health concern (Shafran, 1990). In a recent development, the World

Health Organization (WHO) has identified antibiotic resistance as one of the foremost worldwide public health challenges confronting the human population. It is predicted that antibiotic-resistant infectious diseases will have a global impact, affecting a minimum of 700,000 individuals each year. Projections indicate that by the year 2050, these infections could be responsible for around 10 million fatalities a year and cause significant economic damage on a global scale (Coates et al., 2020).

The effective management and control of gonorrhoea are impeded by the extensive resistance exhibited by the varied strains of *Neisseria gonorrhoeae*. The emergence of resistance to sulfonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early cephalosporins has occurred at a rapid pace. In the present context, it is widely acknowledged that ceftriaxone stands as the sole empirical monotherapy for the treatment of gonorrhoea in the majority of nations. Antimicrobial resistance is a multidimensional and intricate issue that is influenced by a range of circumstances (Uddin et al., 2021):

a. The augmentation of bacterial population density within healthcare facilities facilitates the transmission of bacteria to the wider community.
b. The hospital's failure to comply with hygiene procedures and regulations aimed at maintaining cleanliness contributes to the escalation of antimicrobial resistance (AMR) in bacteria.
c. The overutilization of antibiotics in the agricultural sector.
d. International travel and trade can potentially lead to the dissemination of germs that are resistant to dispersion.
e. In certain regions, there is an insufficiency in sanitation practices, resulting in the potential contamination of water systems and the dissemination of antibiotic-resistant bacteria within sewage networks.
f. The excessive utilization of antibiotics in the field of human medicine, such as their application for the treatment of viral illnesses that are contagious in nature.
g. The absence of prompt diagnostic methods to facilitate the judicious administration of antibiotics is one of the key issues.

The degree of resistance expression, the microorganism's tolerance of resistance mechanisms, the place of initial colonization, and other host variables all play a role in the formation of an antimicrobial-resistant phenotype. When the factors that determine resistance are found on plasmids, they spread quickly within bacterial genera and sometimes even between different bacterial genera. Microorganisms with resistance that is connected to chromosomal genes will proliferate more slowly (Stratton, 2000). An important cause of the spread of antimicrobial resistance is the failure to implement infection control either in the hospital or outside the hospital (WHO, 2016).

The most basic form of resistance is characterized by a diminished natural vulnerability, sometimes referred to as innate resistance. The potential reasons for this occurrence may include the lack of receptors for antibiotics, reduced affinity, impermeability of the cell wall, or the synthesis of enzymes (Urban-Chmiel et al., 2022). Bacteria acquire partial or complete resistance to specific antibiotics through the development of diverse effector mechanisms, which are facilitated by the presence of resistance genes (Darby et al., 2023).

Numerous scientific investigations undertaken since the mid-20th century have elucidated several processes that account for bacterial resistance to antibiotics (Giedraitienė et al., 2011).

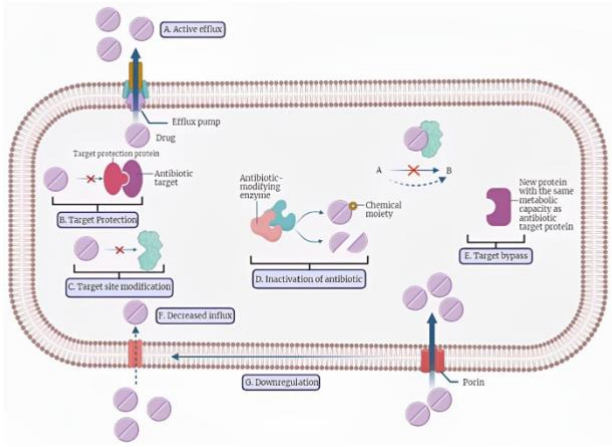


Figure 1: Molecular mechanisms of antibiotic resistance.

A. Active efflux is enabled through an efflux pump located on the transmembrane, which expels antibiotics from the bacterial cell, thereby diminishing their intracellular concentration (Masi & Pagès, 2013).
B. The target becomes protected due to the presence of a protein that protects the antibiotic target, so it is free from antibiotic-mediated inhibition (Doi et al., 2017).
C. Target bypass, the antibiotic target is actually occupied by a new protein that is not inhibited by the antibiotic, so the initial target does not work and the antibiotic is ineffective.
D. Changes in the target location result in changes in the antibiotic's target thereby reducing the binding of the antibiotic. This can occur due to gene mutations that code for protein targets of antibiotic or enzymatic molecules at binding sites (Lambert, 2005).
E. Antibiotics exert their effects by altering the activity of enzymes responsible for transferring diverse chemical groups onto the antibiotic molecule, thereby impeding the binding of the antibiotic to its intended target. Enzymatic degradation refers to the process of hydrolyzing the functional groups of the antibiotic, resulting in its loss of effectiveness (Varela et al., 2021).
F. The reduction in the rate of inflow is facilitated by alterations in the structure of the membrane, namely by the downregulation of porins. Porins are transmembrane proteins responsible for enabling the passive transport of substances into the bacterial cell (Masi & Pagès, 2013).

Based on the background above, we found a problem that we will discuss in this review. First is the pattern of evolution of *N. gonorrhoea*'s resistance to antibiotics: second, what antibiotics can be used as alternative therapies in cases of gonorrhea infections that are resistant to antibiotics.

2. Methods

2.1. Search strategies

The procedure utilized in this systematic review adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, which provides a standardized framework for reporting systematic reviews. A comprehensive literature review was undertaken using PubMed, Embase, Central, and Web of Science. Several keywords were used to find relevant studies: antibiotic-resistance, gonorrhea infection, and randomized controlled trials (RCTs). The initial search was conducted on July 30th, 2023. Inclusion criteria:

- The study that consists of alternative therapy for antibiotic-resistant gonorrhea infection
- The study with a randomized controlled trial study design
- Peer-reviewed article published between 2013-2023

Exclusion criteria:

- The study was a non-randomized controlled trial
- Observational article

- An article that only explains antibiotic resistance

2.2. Data extraction

The titles and abstracts were thoroughly examined to ensure their alignment with the predetermined inclusion criteria. The complete reports were subsequently evaluated to see whether the publications met the inclusion criteria, which encompassed outcomes, interventions, research designs, and patient demographics. The rationales for the exclusion of studies were elucidated.

2.3. Quality assessment

The methodological quality of the research was assessed by two independent reviewers (CVA and CAS) using the Risk of Bias 2 (RoB2) methods. Cochrane Reviews only comprise randomized studies that have undergone evaluation of their risk of bias utilizing the Cochrane risk-of-bias tool for randomized trials, version 2. The defined categories of bias in RoB 2 cover a wide variety of possible issues with trials and their reporting. The goal of a series of inquiries known as "signaling questions" is to obtain information regarding trial characteristics relevant to each domain's risk of bias. An algorithm proposes a bias risk estimate for each domain based on the replies to the signaling questions. Bias risk ratings can vary from "Low" to "High," with "Some concerns" as an option.

2.4. Description of selected studies

The systematic search showed 28 results. Only peer-reviewed English-language publications published between 2013 and 2023 were considered. The datasets underwent a process of removing a single instance of duplicated research. A total of 27 articles were assessed based on their titles and abstracts, resulting in the evaluation of 23 full-text papers. Seventeen studies were eliminated because they had the incorrect setting (n = 6), indication (n = 1), intervention (n = 1), research design (n = 6), and patient population (n = 3). Six studies were considered in this analysis. Please have a look at Figure 2 and Table 1.

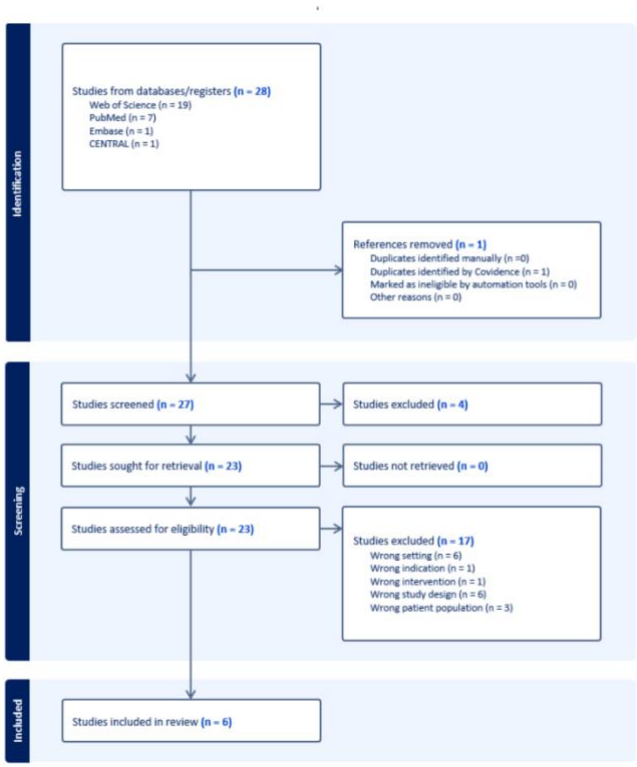
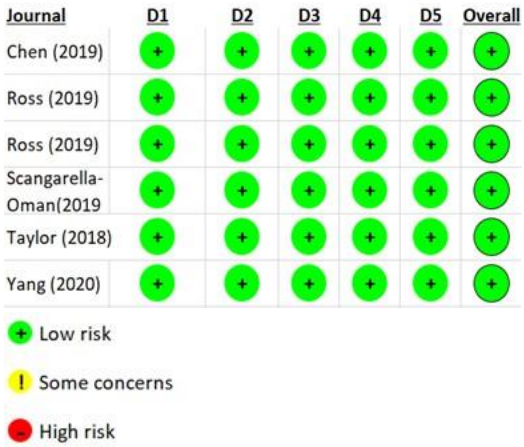


Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram



D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Table 1: Summary of Selected Study Characteristics

No.	Title	Author, year (Country)	Aim of study	Population and Intervention	Result and Outcomes
1.	Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea	(Taylor et al., 2018) (New Orleans)	Evaluated Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea	Total participants: 179 (167 men and 12 women) men and nonpregnant women aged 18 to 55 years urogenital gonorrhea without complication sexual contact within the past 14 days with a person diagnosed with gonorrhea.	141 participants were eligible for evaluation. Result: urogenital infections were successfully cured in a high percentage 2 g of zoliflodacin, 96% (55 out of 57 participants) 3 g of zoliflodacin (96%, 54 out of 56 participants) and ceftriaxone (100%, 28 out of 28 participants). For rectal infections: 2 g of zoliflodacin(5 participants) 3 g of zoliflodacin (7 participants) ceftriaxone group (3 participants. 21 adverse events as being related to zoliflodacin, most of these: gastrointestinal in nature.
2.	Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial	(Ross, Brittain, et al., 2019) (London)	Tho assess whether single-dose gentamicin therapy is an acceptable alternative to ceftriaxone for the treatment of gonorrhea when both antibiotics are combined with azithromycin	720 were enrolled (362 were assigned to receive ceftriaxone and 358 to receive gentamicin) 322 (89%) of 362 participants allocated to ceftriaxone and 302 (84%) of 358 participants allocated gentamicin	The median time from randomization to follow-up was 16 days (IQR 14-20) in the ceftriaxone group and 15 days (IQR 14-20) in the gentamicin group. 267 (83%) of 322 participants in the ceftriaxone group and 248 (82%) of 302 participants in the gentamicin group returned within 21 days. 2 weeks after treatment, the infection had cleared for 299 (98%) of 306 participants allocated to ceftriaxone compared with 267 (91%) of 292 participants allocated to gentamicin (adjusted risk difference -6·4%, 95% CI -10·4% to -2·4%. Gentamicin plus azithromycin cannot be considered non-inferior to ceftriaxone plus azithromycin, with a relatively higher frequency of treatment failure extragenital gonorrhoea who were treated with gentamicin. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gentamicin combined with 1 g azithromycin achieved a cure rate of 94% for genital gonorrhoea might be appropriate in patients who are allergic, intolerant, or harbour a ceftriaxone-resistant infection.
3.	Microbiological analysis from a	(Scangarella-Oman et al.,	Evaluated microbiological	The microbiologically	The success rate was 100% (61/61) when the fAUC/MICs (free drug area under the

	phase 2 randomized study in adults evaluating single oral doses of gepotidacin in the treatment of uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae*	2018) (Alabama, USA)	correlates for the successful treatment of *N. gonorrhoeae* isolates from a phase 2 study of gepotidacin, a novel triazaacenaphthylene antibacterial, for therapy of uncomplicated urogenital gonorrhea.	evaluable population consisted of 69 randomly assigned participants (67 male and 2 female) with culture-confirmed urogenital gonorrhea at baseline who received gepotidacin and returned for TOC. Culture, susceptibility testing, genotypic characterization, and frequency of resistance (FoR) were performed for selected isolates.	concentration-time curve to minimum inhibitory concentration ratio) were at 48, but it decreased to 63% (5/8) when the fAUC/MICs were at 25. 3 were resistant to ciprofloxacin, carried a preexisting ParC D86N mutation. In a test-of-cure analysis, resistance to gepotidacin emerged in two with additional GyrA A92T mutations. For five selected baseline isolates, all carrying the ParC D86N mutation, the in vitro FoR (frequency of resistance) to gepotidacin was low (ranging from 10^9 to 10^10); In conclusion, fAUC/MICs of 48 were associated with 100% microbiological success, even including three isolates with the ParC D86N mutation (fAUC/MICs ≥ 97).
4.	Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: The G-TOG non-inferiority RCT	(Ross, Harding, et al., 2019) (UK)	To provide information on the safety, effectiveness, and cost-effectiveness of gentamicin compared to ceftriaxone for the treatment of gonorrhoea.	Gentamicin compared to ceftriaxone for the treatment of gonorrhoea. It was estimated that a total sample size of 646 participants for analysis (323 in each group) would achieve 90% power at the 2.5% one-sided significance level to detect non-inferiority with a lower 95% confidence interval (CI) for the absolute risk difference of 5%.	1. Primary Outcome: The clearance rate of *N. gonorrhoeae* infection at the pharynx, rectum, and urethra was similar between the gentamicin and ceftriaxone groups. 2. Secondary Outcomes: - Clinical resolution of symptoms: Both gentamicin and ceftriaxone groups showed similar rates at 2 weeks post-treatment. The cost-effectiveness of gentamicin compared to ceftriaxone was evaluated using a decision tree model. The results showed that gentamicin was cost-effective compared to ceftriaxone for the treatment of gonorrhea.
5.	Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial	(Chen et al., 2019) (Australia and USA)	To compare the efficacy and safety of solithromycin with ceftriaxone plus azithromycin for the treatment of gonorrhea.	(1) Total of 262 patients, with 131 : solithromycin group 131 : cefriaxone plus azithromycin group. (2) The majority of patients were men (94%), particularly men who have sex with men (72%). (3) Mean age: 30.1 years in the solithromycin group and 29.4 years in the ceftriaxone plus azithromycin group. (4) Some patients had co-infections with chlamydia at various anatomical sites.	The primary outcome: eradication of genital gonorrhea based on culture at day 7. 80% of patients in the solithromycin group and 84% of patients in the ceftriaxone plus azithromycin group Secondary outcomes: proportion of patients with eradication of gonorrhea based on culture at day 7 at each anatomical site, clearance of gonorrhea based on NAAT at day 7, and clearance of chlamydia based on NAAT at day 21. The study found that solithromycin was non-inferior to ceftriaxone plus azithromycin in achieving these secondary outcomes. Adverse events were similar between the two treatment groups, with gastrointestinal events being the most common.
6.	Evaluation of alternative antibiotics for susceptibility of gonococcal isolates from China (2019)	(Yang et al., 2020) (China)	To evaluate the susceptibility of *N. gonorrhoeae* isolates from China to alternative antibiotics	The population in this study consisted 504 clinical isolates of *N. gonorrhoeae* obtained from seven hospitals in Zhejiang province, China The intervention in this study involved evaluating the susceptibility of these isolates to alternative antibiotics	Among the 504 clinical isolates there was a high prevalence of decreased susceptibility to ceftriaxone and resistance to azithromycin. Tigecycline and ertapenem showed potential as alternative antimicrobials for the treatment of gonorrhea. Tigecycline and ertapenem could be considered as potential options for single or dual therapies, possibly in combination with ceftriaxone. Need for further research and clinical trials to evaluate the efficacy of these alternative antibiotics in the management of gonorrhea.

3. Discussion

3.1. Evolution of Antimicrobial Resistance

The bacterium *Neisseria gonorrhoeae* has exhibited the emergence of resistance to antibiotic treatment. The rise of strains that are resistant to ceftriaxone poses a significant threat to the limited remaining therapeutic options available. The development of the Gonococcal Resistance to Antimicrobials Surveillance Programme Action Plan (GRASP) in 2013 aimed to mitigate the proliferation of antimicrobial resistance (AMR) in England. The period spanning from 2013 to 2019 witnessed a substantial increase in the incidence of gonorrhoea cases in the United Kingdom, with a surge of 128% resulting in a record-breaking annual figure of 70,922 diagnoses (Lawrence et al., 1973). Antimicrobial resistance to sulfonamide, macrolides (including azithromycin), penicillin, tetracylin, quinolones, and even ceftriaxone as a first line therapy has been documented in a significant proportion of the gonococcal population with depressing regularity over extended periods. In the worst-case scenario, gonorrhea may become untreatable (Tapsall et al., 2009). (Figure 3)

3.2. Sulfonamides

The utilization of sulfonamides as a therapeutic intervention for the treatment of gonorrhoea was first introduced in the 1930s. Nevertheless, it was documented that in 1944, a significant proportion of World War II soldiers engaged in the Italian and Sicilian campaigns saw a treatment failure rate of 75% when administered with sulfathiazole or sulfapyridine (Campbell & Ed, 1944).

During the 1960s, a proposal was made to enhance the effectiveness of sulfonamide in the treatment of simple gonorrhoea by implementing a combined therapy involving trimethoprim. Until the 1970s, the therapeutic approach for treating gonorrhoea was the utilization of sulfonamides in conjunction with trimethoprim, which was found to exhibit a synergistic effect. This treatment regimen involved the administration of high doses of the combined drugs at many intervals (Lawrence et al., 1973).

3.3. Penicillin

The utilization of penicillin as an antibacterial therapy for gonorrhoea commenced in 1943. Nevertheless, the effectiveness of penicillin against gonococcus began to decline in the 1960s. Penicillin, functioning as a β-lactam antimicrobial agent, exerts its inhibitory effect on the formation of bacterial cell walls by specifically binding to transpeptidase enzymes known as penicillin-binding proteins (PBP) located in the periplasmic space. In the initial five decades of penicillin utilization, the development of resistance mechanisms in the gonococcus bacterium was observed to be associated with a decline in susceptibility. This decline was attributed to the accumulation of chromosomal mutations in various genes involved in the biosynthesis of the cell wall (penA and ponA1), as well as structures that impact the concentration of drugs in the periplasmic space (penB, penC, and mtrR) (Lobanovska & Pilla, 2017).

3.4. Tetracycline

The introduction of tetracycline in the 1950s provided an alternative treatment for people with gonorrhoea who exhibited allergic reactions to penicillin. The protein synthesis process is impacted by the antimicrobial agent through its interaction with the 30S ribosomal subunit. Just as with the development of resistance to penicillin, resistance to tetracycline emerged gradually over time. Indeed, certain chromosomal changes associated with resistance to penicillin, such as penB and mtr overexpression, have been found to hinder the effectiveness of tetracycline (Unemo & Shafer, 2014).

The initial identification of gonococcus isolates exhibiting high-level resistance to tetracycline was seen in the United States in 1985. The mechanism underlying the resistance phenotype, which shields the ribosome from tetracycline binding, has been elucidated with the identification of the TetM protein. The emergence of resistance

in the treatment of gonorrhoea during the quinolone period can be traced back to the discontinuation of tetracycline as a suggested therapeutic option in the mid-1980s (Costa-Lourenço et al., 2017).

3.5. The quinolone era in gonorrhea treatment

The development of ciprofloxacin occurred in 1983. In the early stages, the treatment of gonorrhoea involved the administration of ciprofloxacin in a single dose of 250 mg. Nevertheless, due to initial reports of reduced effectiveness, the initial recommendation from the Centers for Disease Control and Prevention (CDC) for ciprofloxacin treatment of this sexually transmitted infection (STI) was a single dose of 500 mg (Unemo & Shafer, 2014).

Quinolones exert their influence on DNA gyrase and topoisomerase IV, two crucial topoisomerases involved in several cellular processes such as DNA replication, transcription, recombination, and repair. This category of antimicrobial medicines functions by creating a complex including the drug, enzyme, and DNA, resulting in the release of double-strand DNA breaks. The resistance of *N. gonorrhoeae* to ciprofloxacin is facilitated by genetic changes occurring in the quinolone resistance-determining region (QRDR), which is situated in close proximity to the DNA binding site of the topoisomerases. These alterations collectively impact the susceptibility of isolates. Mutations resulting in a singular alteration of a single amino acid at positions 91 or 95 in the GyrA protein are associated with an intermediate level of resistance. However, when three or more amino acid changes occur at positions 91, 95, and 102 in the GyrA protein, as well as at positions 87 and 91 in the ParC protein and position 439 in the ParE protein, higher levels of resistance are observed (Hooper & Jacoby, 2016).

Ciprofloxacin treatment, which was first recommended as the primary treatment for gonorrhoea in the United States, was discontinued in the Asian Western Pacific region due to the emergence of significantly elevated resistance rates. In the context of Japan, it is noteworthy that the rate of resistance stood at 6% during the period of 1993–1994, and then experienced a significant increase to 24% in the years 1997–1998 (Costa-Lourenço et al., 2017).

3.6. Azithromycin

The inclusion of azithromycin as a potential therapeutic option for the treatment of gonorrhoea began in the early 1980s. This particular macrolide compound exhibits an interaction with the P site of the 50S ribosomal subunit, resulting in the inhibition of the peptidyl transferase activity and subsequent impairment of the elongation process of the polypeptide chain (Zarantonelli et al., 1999).

One of the factors contributing to the increased resistance of *N. gonorrhoeae* to penicillin and enhanced sensitivity to azithromycin is the upregulation of the efflux pump mtrCDE. This upregulation is mediated by the same molecular pathways previously described to reduce susceptibility to penicillin. Another way in which azithromycin decreased susceptibility might emerge is through the presence of mutations in the L4 ribosomal protein. The protein in question exhibits close proximity to the peptidyl-transferase area located inside the V domain of the 23S rRNA. Mutations that result in significant alterations to the amino acid sequence, such as the G70D mutation observed in its extended loop, have the potential to indirectly influence the conformation of the rRNA. In recent years, there has been an emergence of *N. gonorrhoeae* strains that demonstrate a significant degree of resistance to azithromycin. The initial instance transpired in Argentina during the year 2001 (Zarantonelli et al., 1999).

3.7. Ceftriaxone

The extended-spectrum cephalosporin ceftriaxone exhibits significant efficacy against gram-negative bacteria, particularly *N. gonorrhoeae*, through its strong binding affinity to penicillin-binding protein 2 (PBP2). The utilization of ceftriaxone as a standalone treatment for gonococcal infections emerged in response to the increasing prevalence of ciprofloxacin resistance. Cefixime, an oral extended-spectrum cephalosporin (ESC), was employed prior to the introduction of ceftriaxone. Nonetheless, the efficacy of this antibacterial agent diminished rapidly (Fenton et al., 2021).

The development of resistance to extended-spectrum cephalosporins (ESC) may be facilitated by genetic modifications in the penB, mtrR, and penC genes. However, it is primarily mutations in the penA gene, responsible for encoding penicillin-binding protein 2 (PBP2), that appear to be the primary determinant of ceftriaxone resistance. The modified penA gene can arise due to point mutations or by genetic recombination between commensal *Neisseria spp*. that inhabit different human sites, leading to the formation of a mosaic-like structure. The modified penicillin-binding protein 2 (PBP2) exhibits reduced binding affinity towards ceftriaxone (Fenton et al., 2021).

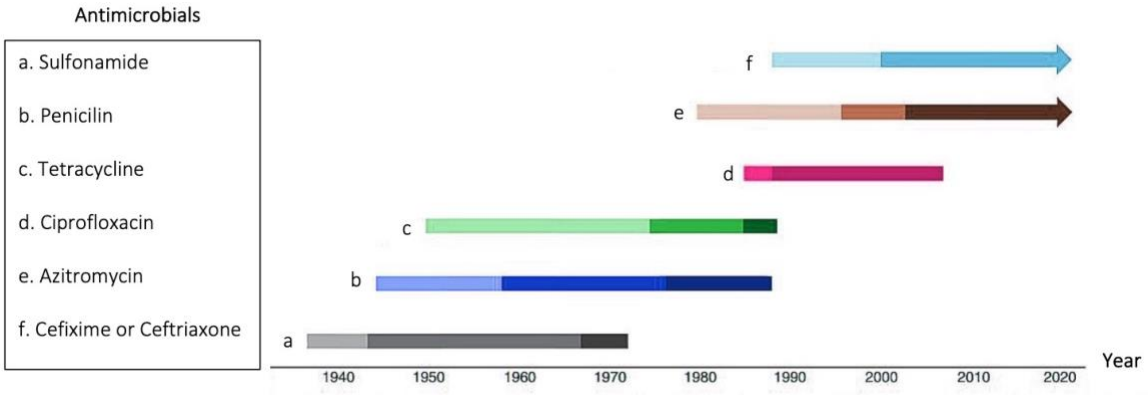


Figure 3: The phenomenon of antibiotic resistance in *Neisseria gonorrhoeae*. The color changer serves as an indicator of events that have negatively impacted the efficacy of antimicrobial agents over time, leading to a decrease in their resistance levels. Sulfonamide: an introduction, incidence of resistance, co-administration with trimethoprim: penicillin and tetracycline: an introduction, chromosomally-mediated resistance, plasmid-mediated resistance: ciprofloxacin: an introduction, reported resistance: azithromycin: an introduction, reported resistance, high-level resistance: cefixime or ceftriaxone: an introduction, reduced susceptibility reported.

4. Various Effective Therapeutic Antibiotics are used to Overcome Resistance in Gonorrhea

The development of alternative antimicrobial therapy is urgently needed to ensure that gonorrhea treatment remains available in the future. From various studies aimed at treating gonorrhea that is resistant to antibiotics, the effectiveness of these antibiotics is considered to be a solution to gonorrhea resistance. These antibiotics are zoliflodacin, ceftriaxone, gentamicin, gepotidacine, solithromycin, tigecycline, and ertapenem.

4.1. Gentamicin

In recent years, gentamicin has emerged as a prominent alternative antimicrobial agent for combating resistant gonorrhea. Extensive research efforts have been dedicated to investigating the efficacy of gentamicin in various clinical trials, both as a component of dual therapy and, more recently, as a standalone treatment option. Gentamicin is an aminoglycoside antibiotic that binds to 30S ribosomal subunits in an irreversible manner to prevent protein synthesis (Ross, Brittain, et al., 2019). The utilization of this treatment has been observed in numerous developing nations for the management of gonorrhoea, offering the distinct advantage of exhibiting both notable therapeutic efficiency and cost-effectiveness (Liu et al., 2019). The gonorrhea-causing bacterium *Neisseria gonorrhoeae* is inhibited from synthesizing proteins by the aminoglycoside drug gentamicin. To accomplish this, it binds to the decoding location where the 30S ribosomal subunit of bacteria is located, disrupting protein synthesis and causing bacterial death. It has been demonstrated that gentamicin can successfully treat gonorrhea, especially when combined with other antibiotics such as azithromycin or ceftriaxone. The development of medication resistance may be slowed down with the use of this combination therapy (Xu et al., 2022). (Figure 4)

In areas with limited resources, gentamicin is an affordable antibiotic used to treat genital gonorrhoea infections. Studies conducted in Malawi reveal that gonococcal isolates are very susceptible to gentamicin, with 95% clinical cure rates when coupled with doxycycline (Hathorn et al., 2014). Gentamicin has been proposed as an alternative

treatment option to ceftriaxone in guidelines issued by the American, European, and World Health Organization (WHO). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) do not provide any established criteria for determining the resistance of *Neisseria gonorrhoeae* to gentamicin. A point mutation in the fusA gene, responsible for encoding the elongation factor G (EF-G), results in a missense mutation that leads to an A563V substitution specifically in the IV domain of EF-G. The alternative form of the gene, known as fusA2, was designated as the mutant allele (Mlynarczyk-Bonikowska et al., 2022). In a study conducted by Holley et al., it was demonstrated that fusA2 has the ability to elevate the minimum inhibitory concentration (MIC) of gentamicin by a factor of four, resulting in a MIC value of 32 mg/L. While the presence of fusA2 did not hinder the development or protein synthesis of gonococci in vitro, it did result in a decrease in fitness when the lower vaginal tract of female mice was experimentally infected (Holley et al., 2022).

According to Ross et al, 2019, it is not suggested to substitute ceftriaxone with gentamicin as the first-line therapy for gonorrhoea. Nonetheless, the combination of gentamicin and 1 g azithromycin demonstrated a cure rate of 94% for genital gonorrhoea. This treatment option could be considered suitable for people who exhibit allergies, intolerances, or are afflicted with a ceftriaxone-resistant illness (Ross, Brittain, et al., 2019).

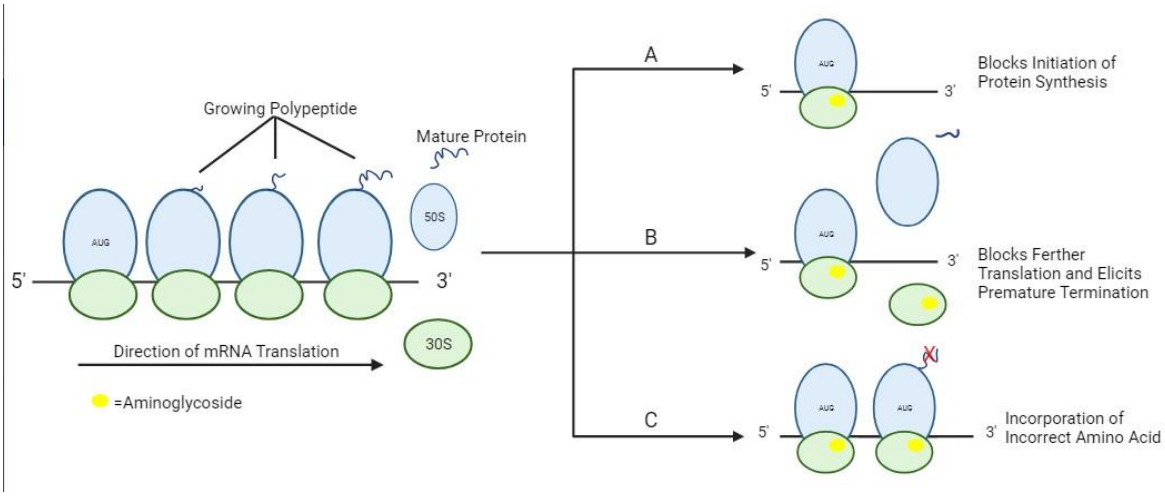


Figure 4: Impact of aminoglycosides on the process of protein synthesis. A. Aminoglycosides, shown as red circles. This interaction disrupts the initiation phase of protein synthesis by stabilizing the 30S–50S ribosomal complex at the mRNA start codon (AUG). Accumulation of aberrant initiation complexes inhibits the continuation of mRNA translation downstream. Binding of aminoglycosides to the 30S ribosomal subunit has been observed to induce the phenomenon of mRNA misreading, resulting in B. Premature end of translation, characterized by dissociation of the ribosome complex and production of a completely unsynthesized protein C. Insertion of the wrong amino acid (denoted by a red X) causes synthesis anomalous or dysfunctional proteins.

4.2. Ceftriaxone

The increasing prevalence of gonococcal resistance to non-cephalosporin categories of antimicrobial drugs has necessitated the utilization of cephalosporins, namely the administration of ceftriaxone via intramuscular injections and cefixime orally. However, trends in increasing mean minimum inhibitory concentrations (MICs) of *N. gonorrhoeae* for both agents, indicating decreasing susceptibility, have been reported worldwide and have led to changes in the recommendations for use of these agents. Research conducted by Ross et al., 2019 shows that the clearance rate of *Neisseria gonorrhoeae* infection at the pharynx, rectum, and urethra was similar between the gentamicin and ceftriaxone groups. Ceftriaxone is a pharmacologically potent bactericidal agent that functions by interfering with the process of bacterial cell wall synthesis, hence playing a crucial role in efficiently combating a wide range of diseases. By specifically binding to penicillin-binding proteins, it has the ability to thwart the activities of penicillinase and cephalosporins, which ensures its efficacy against both Gram-negative and Gram-positive bacterial strains. When administered, ceftriaxone attaches itself to the penicillin-binding proteins present in bacterial cells, thereby impeding the final transpeptidoglycan step crucial for peptidoglycan synthesis in the cell

wall. This crucial interruption leads to the inhibition of cell wall assembly and, consequently, the death of bacterial cells (Bereda, 2022). (Figure 5)

Ceftriaxone, a potent third-generation cephalosporin with extended-spectrum activity, boasts an impressive cure rate ranging from 72% to 97% and demonstrates exceptional efficacy against both gram-negative and gram-positive bacteria. This antimicrobial agent has been widely used in healthcare facilities over the last two decades, often prescribed for empirical treatment to address diverse infections. A quarter-century-old study sought to investigate the incidence of bacterial species and their responses to ceftriaxone and other lactam antibiotics in people with community-acquired illnesses (Tewabe et al., 2021).

In gonococci, β-lactam antibiotics encounter resistance through rapid plasmid-mediated β-lactamase production and gradual chromosomal gene mutations. Ceftriaxone resistance is linked to extended-spectrum β-lactamase production in E. coli and the presence of specific β-lactamases in Salmonella isolates. These mechanisms play a significant role in the spread of cephalosporin resistance, particularly ceftriaxone (Tewabe et al., 2021).

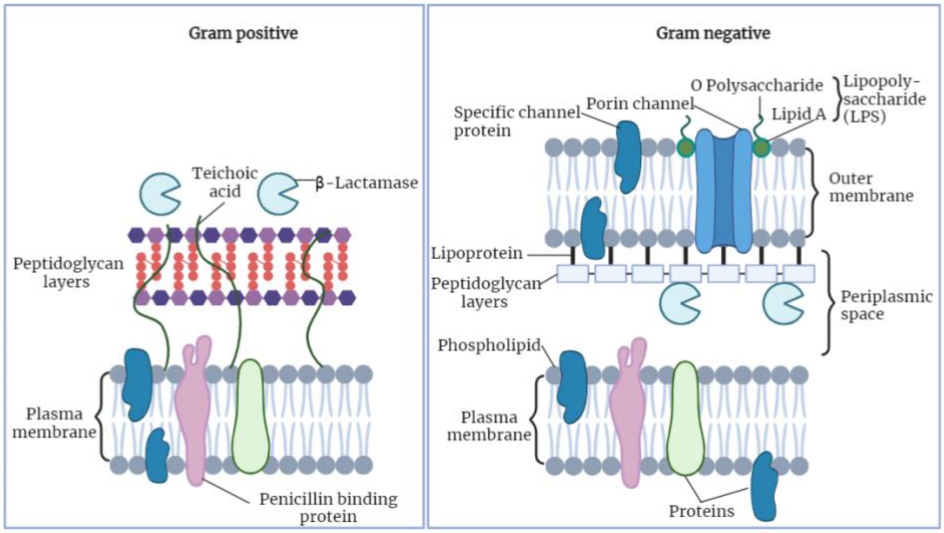


Figure 5: Structure and composition of gram-positive and gram-negative cell walls. Ceftriaxone acts as a transpeptidase enzyme that inhibits the transpeptidation reaction and then inhibits the synthesis of peptidoglysin. Activation of the autolytic enzymes causes an increase in cell membrane permeability, resulting in cell bursting and lysis.

4.3. Gepotidacin

In early clinical trials, gepotidacin, a novel antibiotic, has shown promising results for the treatment of urinary tract infections (UTIs), urogenital gonorrhea. It was developed in response to the rising bacterial resistance to fluoroquinolone drugs such as ciprofloxacin. This is a type of antibiotic known as triazaacenaphthylene, and how it works like fluoroquinolones is to stop bacterial DNA replication by stopping two important topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV. The presence of these enzymes is crucial for the processes of DNA repair and replication in bacteria, and they are responsible for unwinding and resealing DNA strands during replication, which ensures the proper separation and organization of the DNA. It is unclear how gepotidacin resistance manifests in gonorrhea. The target enzymes gepotidacin, DNA gyrase and DNA topoisomerase IV, are thought to be susceptible to changes that might lead to treatment resistance. Gepotidacin's ability to limit DNA replication by diminishing its binding affinity to the target enzymes has been demonstrated in studies to be diminished by mutations in these genes, which can also result in resistance (Ross, Brittain, et al., 2019). (Figure 6)

The quinolone resistance-determining regions (QRDRs), which are recognized hotspots for resistance mutations in quinolone antibiotics, are one such area of the genes where these mutations might arise. Given that gepotidacin

is still in its early phases of development and clinical trials, it is significant to highlight that resistance to the medicine is not yet pervasive in gonorrhea. However, to guarantee the long-term efficacy of gepotidacin against gonorrhea, ongoing monitoring of resistance patterns and observation of infection trends will be essential (Unemo

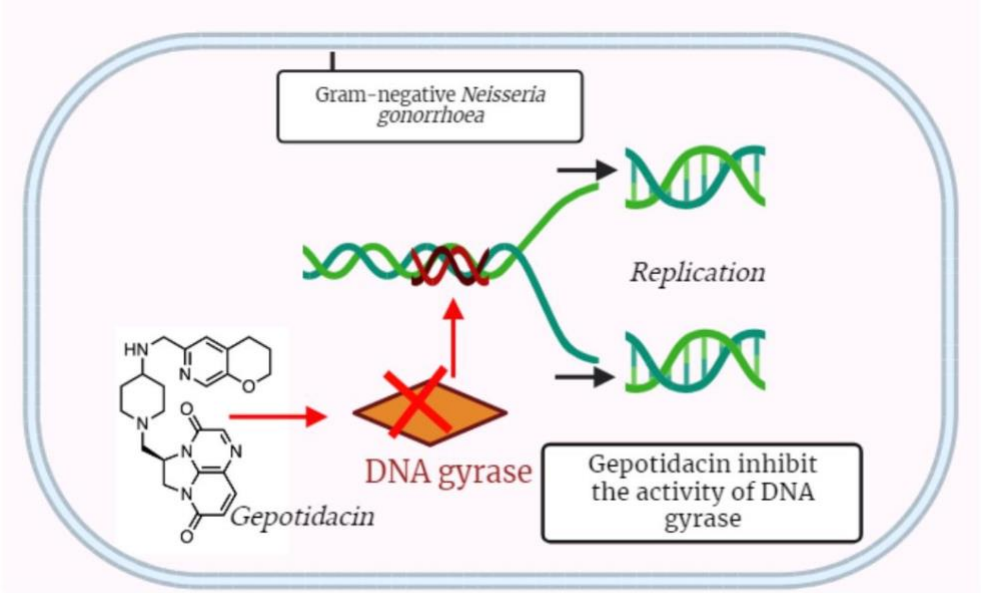


Figure 6: Gepotidacin functions by inhibiting the activity of gyrase in *N. gonorrhoea* and topoisomerase IV in gram-positive bacteria. This inhibition occurs through the formation of a complex involving the drug, the enzyme, and DNA. As a result, the drug is able to impede the normal functioning of these enzymes, leading to the generation of deadly double-stranded DNA breaks upon subsequent release. The breakage of these strands initiates the SOS response, which then triggers a DNA repair mechanism characterized by the involvement of low fidelity DNA synthesis. This process can result in the occurrence of deadly mutations, leading to genomic toxicity and ultimately culminating in cell death.

4.4. Zoliflodacin

In response to the persistent medical challenge posed by multi-drug resistance *N. gonorrheae*, researchers have created zoliflodacin, a novel class of antibacterial medicines referred to as spiropyrimidinetriones, with the aim of addressing simple gonorrhea. Zoliflodacin is an antibacterial medication that can be administered orally and exhibits bactericidal effects against bacterial type II topoisomerases. DNA topoisomerases are a class of enzymes found within cells that play a crucial role in the regulation of the three-dimensional conformation of DNA molecules within the nucleus. The differentiation between topoisomerase types I and II lies in their ability to create temporary single-or double-stranded breaks in DNA. Despite exhibiting significant similarities in sequence and structure, these enzymes serve separate roles in the process of DNA replication. Topoisomerase IV and DNA gyrase are a pair of closely affiliated DNA topoisomerase type II enzymes that play an essential role in DNA synthesis and serve as the primary targets of fluoroquinolones. These enzymes work together to induce changes in the structure of DNA throughout the process of replication. They begin by unwinding the tightly coiled DNA strands, then create temporary breaches in the double-stranded DNA, and finally reseal the breaks. DNA gyrase is a protein complex composed of two subunits, GyrA2-GyrB2, which functions to modulate the negative supercoiling of bacterial DNA. The decatenation (unlinking) of duplicated daughter chromosomes during replication is facilitated by TopoIV, which exists as a heterotetramer composed of ParC2 and ParE2 subunits (Bradford et al., 2020).

Zoliflodacin demonstrated a preferential inhibition of DNA formation over other macromolecules in logarithmically mature bacterial cells. Additionally, it stimulated the SOS response to DNA damage in Escherichia coli at levels comparable to ciprofloxacin. The inhibitory activity of zoliflodacin on bacterial topoisomerases was elucidated by its ability to hinder gyrase-mediated supercoiling and topoisomerase IV-mediated decatenation. Additionally, zoliflodacin was found to stabilize the enzyme-DNA cleaved complex for both gyrase and topoisomerase IV in purified *N. gonorrheae* enzymes. In contrast to ciprofloxacin, the religation process of cleaved

DNA was not observed in the presence of zoliflodacin when magnesium ions were absent from the DNA-gyrase-inhibitor complex (Bradford et al., 2020).

The primary focus of zoliflodacin in *N. gonorrheae* was found to be GyrB, as evidenced by a series of studies utilizing mutants at both the first and second steps. The incidence of zoliflodacin resistance was determined to be remarkably low in a single-step frequency analysis. Amino acid alterations in a conserved area of GyrB are observed in both first- and second-step mutants. Molecular modeling analysis revealed that the modifications leading to decreased susceptibility to zoliflodacin were located within the fluoroquinolone binding site. However, it should be noted that these mutations were primarily observed on the GyrB side of the pocket, in contrast to the more commonly reported fluoroquinolone mutations found on the opposite side in GyrA. Following the process of selecting for zoliflodacin resistance, a comparable series of mutations was observed in the gyrase of Staphylococcus aureus (Bradford et al., 2020).

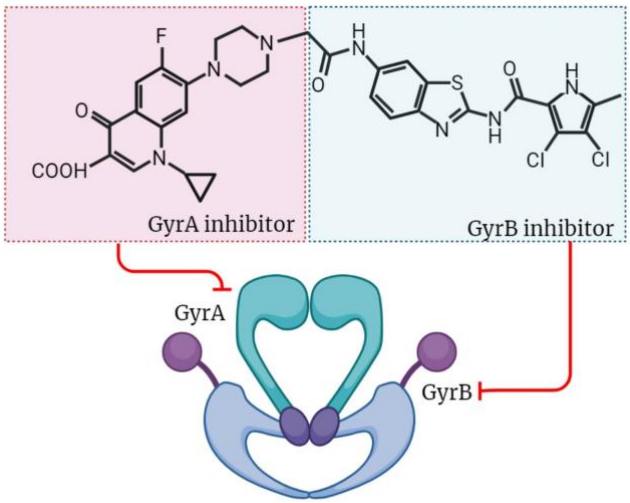


Figure 7: Zoliflodacin targets a “traditional” antibacterial mechanism in a novel way.

4.5. Solithromycin

Solithromycin is a fluoro-ketolide-based fourth-generation macrolide that was intended to replace telithromycin. Solithromycin has a similar structure to telithromycin. Solithromycin is more active against bacterial strains with the erm gene because it does not produce iMLSB-mediated rRNA methylation, it can inhibit cMLSB via the third binding site and the C3 ketone group, and it can adhere to the ribosome more strongly than the prior macrolide (Habiburrahman et al., 2020).

The 50S RNA proteins L4 and L22 normally bind to domain I of 23S rRNA, but mutations in these proteins can produce macrolide resistance by changing the conformation of domains II, III, and V, interrupting macrolide action on domain V of 23S rRNA. Previous research confirmed that mutations in the rrl gene inside the peptidyltransferase loop of domain V of the 23S rRNA generated macrolide resistance in *N. gonorrhoeae*. Solithromycin has a strong affinity for the major bacterial subunit ribosome, which is made up of rRNA residues. This initial contact can decrease protein synthesis by inhibiting polypeptide escape pathways via the exit tunnel. Biochemical analysis and X-ray crystallography reveal significant interactions between solithromycin and rRNA binding sites. Strong drug binding to the ribosome is caused by second contacts between the alkyl-aryl arm of solithromycin with base pairs and hydrogen bonding at the aminophenyl terminus with domain II rRNA 23S (Habiburrahman et al., 2020).

Furthermore, solithromycin binding at several bacterial ribosomal locations can help avoid antibiotic resistance. Solithromycin inhibits and interferes with bacterial protein synthesis with excellent selectivity. At a certain dose, solithromycin can suppress the production of bacterial firefly luciferase (Lux), but it has no impact on luciferase synthesis in the eukaryotic cell translational system. Solithromycin has the ability to interrupt cellular synthesis

and cause the generation of non-functional peptides. Because of these processes, solithromycin is bactericidal, unlike most other macrolide-grade antibiotics (Habiburrahman et al., 2020). (Figure 8)

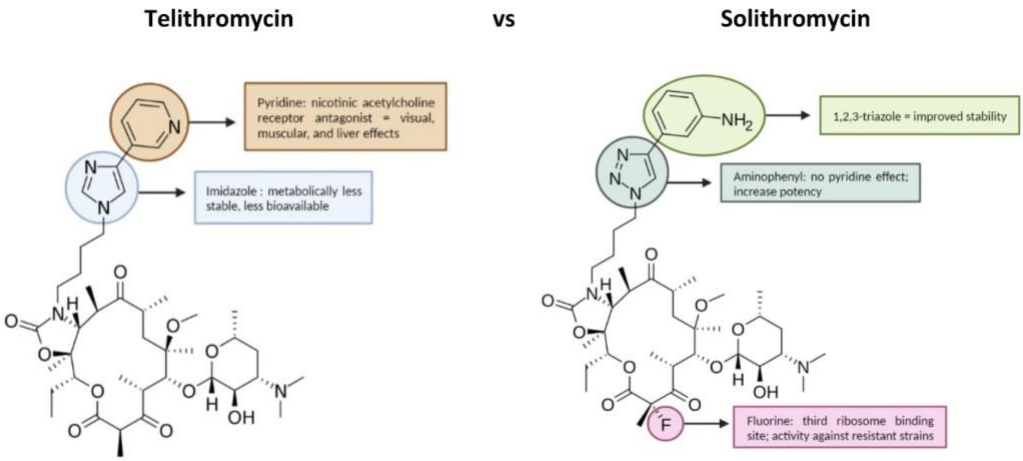


Figure 8: Solithromycin represents the initial instance of a "pure" ketolide. The recognition of the significance of incorporating a 2-F addition in solithromycin, resulting in increased activity against telithromycin-resistant bacteria, led to its classification as a fourth generation macrolide and the first fluoroketolid.

4.6. Tigecycline

Tigecycline, a member of the glycylcycline class of antibiotics, exerts its mechanism of action primarily by targeting the bacterial ribosome, specifically the 30S ribosomal subunit. The drug's unique structure allows it to bind to the ribosome in a manner distinct from traditional tetracyclines, offering increased potency against a wide range of pathogens, including multidrug-resistant organisms. Upon entering the bacterial cell, Tigecycline diffuses across the cytoplasmic membrane and reaches the ribosomes, which are responsible for protein synthesis. It binds to the A site of the 30S ribosomal subunit, preventing the binding of aminoacyl-tRNA, an essential component for the elongation of the growing peptide chain during translation. By doing so, Tigecycline effectively inhibits the incorporation of new amino acids into the nascent polypeptide chain, effectively halting protein synthesis (Yaghoubi et al., 2022). Moreover, Tigecycline exhibits a wide range of antimicrobial action, targeting both Gram-positive and Gram-negative bacteria. This includes very concerning pathogens like Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus (VRE), and Carbapenem-resistant Enterobacteriaceae (CRE) (Yaghoubi et al., 2022). (Figure 9)

A journal examining gonococcal isolates from China has tested the use of tigecycline as an alternative in the treatment of gonorrhea. The results showed that the mode and MIC90 (Minimal Inhibitory Concentration 90) of tigecycline (0.125 mg/L and 0.25 mg/L) were lower than those of doxycycline (1 mg/L and 16 mg/L) and tetracycline (2 mg/L and 64 mg/L). This suggests that tigecycline has stronger antimicrobial activity against gonococcal isolates, indicating the potential of this drug as an effective and reliable treatment option to overcome gonorrhea that is resistant to other antibiotics. These findings provide important insights in the effort to overcome antibiotic resistance and offer therapeutic alternatives that could potentially streamline the treatment of gonorrhea in the future (Yang et al., 2020).

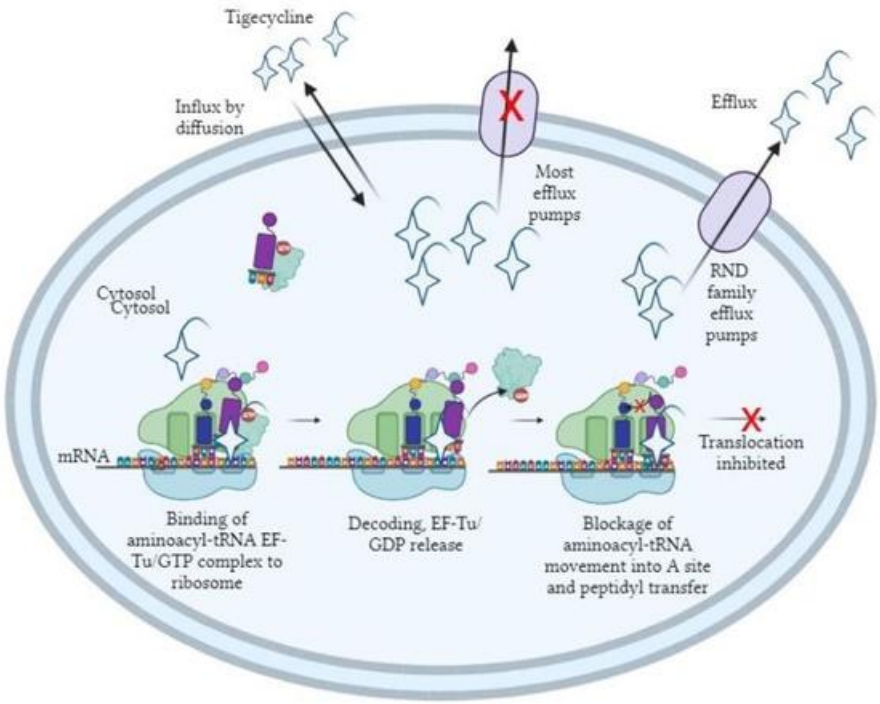


Figure 9: The disruption of protein synthesis leads to a cascade of events within the bacterial cell, ultimately resulting in impaired growth and replication. Tigecycline's ability to target the ribosomal subunit in this novel manner confers its effectiveness against bacteria that have developed resistance to other classes of antibiotics.

4.7. Ertapenem

Ertapenem, a member of the carbapenem class of antibiotics, exerts its mechanism of action by interfering with bacterial cell wall synthesis, leading to cell death. This β-lactam antibiotic demonstrates a broad-spectrum of activity against a diverse array of both Gram-positive and Gram-negative bacteria, rendering it a viable and efficacious therapeutic choice for a multitude of infections(*National Center for Biotechnology Information (2023)*, 2022).

The bactericidal activity of ertapenem is particularly effective against actively growing and dividing bacteria, making it a potent weapon against susceptible pathogens. Additionally, ertapenem demonstrates stability against many β-lactamases, including extended-spectrum β-lactamases (ESBLs) and some AmpC β-lactamases, which are enzymes responsible for antibiotic resistance. However, it is essential to note that ertapenem is not active against metallo-β-lactamases, such as New Delhi metallo-β-lactamase (NDM-1), which can confer resistance to carbapenems. Research has shown that ertapenem exhibits a strong affinity for various PBPs in Escherichia coli, including PBPs 1a, 1b, 2, 3, 4, and 5, with a specific preference for PBPs 2 and 3. By targeting these essential PBPs and inhibiting their transpeptidase activity, ertapenem disrupts peptidoglycan cross-linking in the bacterial cell wall, leading to damage and bacterial cell lysis. The wide spectrum of activity against various bacterial types, coupled with its ability to combat infections caused by multidrug-resistant pathogens, highlights ertapenem's potential as an effective therapeutic agent in the battle against antimicrobial resistance (Zhou et al., 2022).

A journal examining gonococcal isolates from China conducted a trial to evaluate the effectiveness of using tigecycline and ertapenem as alternatives in the treatment of gonorrhea. The results were interesting, with a mode and MIC90 (Minimal Inhibitory Concentration 90) of 0.03 mg/L and 0.06 mg/L respectively, ertapenem showed higher sensitivity than ceftriaxone (0.06 mg/L and 0.125 mg/L) and cefixime (0.06 mg/L and 0.125 mg/L) against these strains. These findings suggest tigecycline and ertapenem have the potential to be single or dual therapy options, possibly in combination with ceftriaxone, and should be considered for further sensitization studies and possibly further clinical trials. The use of these two antimicrobials as alternative gonorrhea treatment options could play an important role in addressing the issue of antibiotic resistance and improving the successful treatment of this infection (Yang et al., 2020).

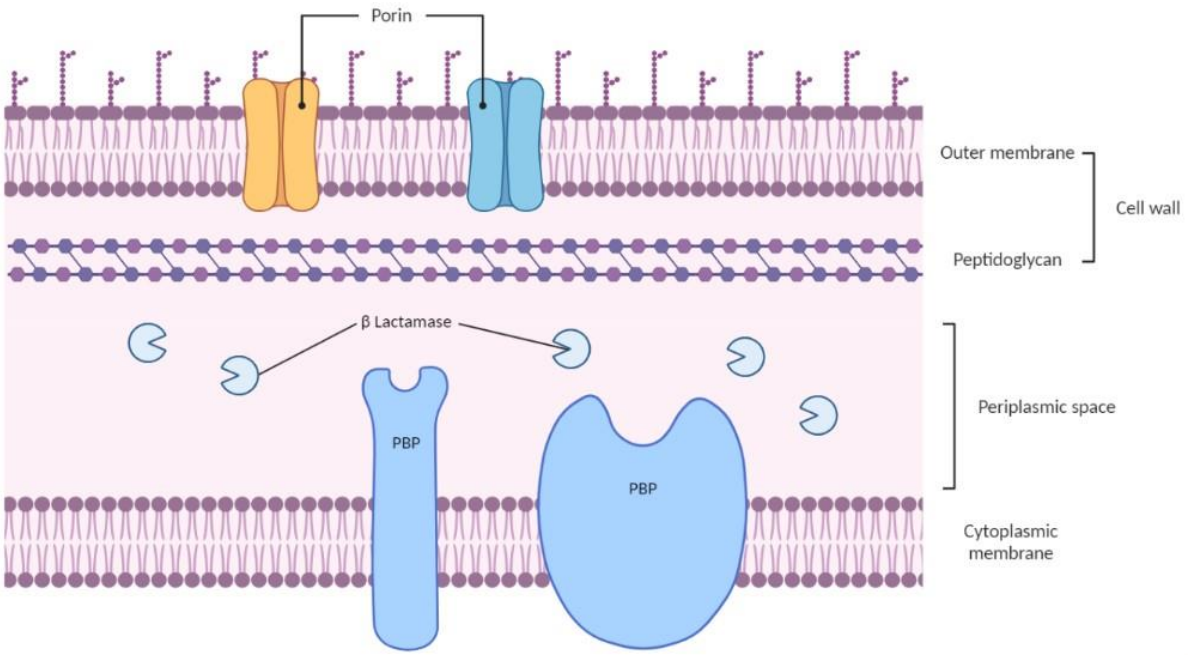


Figure 10: Upon entering the bacterial cell, ertapenem binds irreversibly to penicillin-binding proteins (PBPs), crucial enzymes involved in cell wall formation. Its high affinity for PBP-2, a transpeptidase responsible for cross-linking peptidoglycan chains, disrupts the cross-linking process and weakens the bacterial cell wall. As a result, cell wall damage occurs, followed by cell lysis, ultimately leading to bacterial death.

5. Various Efforts to Develop Types of Antibiotics to Prevent Resistance

The MtrCDE multidrug efflux pump is a significant factor in the development of gonococcal antimicrobial resistance, which results in non-specific resistance to many medications such as penicillins, cephalosporins, azithromycin, tetracyclines, ciprofloxacin, and other hydrophobic or amphipathic substances. Specifically, the emergence of multi-drug resistance in *N. gonorrhoeae* has been linked to certain mutations that suppress the MtrCDE efflux pump. These changes include adenine deletions in the promoter region of the mtrRCDE operon, as well as A39T or G45D polymorphisms in the MtrR protein. Furthermore, it has been observed that the mosaic mtrRCDE allele derived from Neisseria meningitidis and Neisseria commensal species plays a role in the development of multidrug resistance. It is worth noting that there has been a suggestion to sensitize *Neisseria gonorrhoeae* to currently available antibiotics and perhaps to antimicrobial chemicals produced by the human host by targeting MtrCDE through the suppression of its expression. Furthermore, it has been observed that alterations in the primary outer membrane porin not only decrease entry but also enhance efflux. The PorB1b protein has been demonstrated to enhance the level of resistance against penicillins, cephalosporins, and tetracyclines. Specifically, the introduction of mutations at positions G120 and A121 in the porin constriction zones, where bigger charged residues are substituted, has led to elevated levels of resistance (Golparian et al., 2014).

Efflux pumps are a class of membrane proteins responsible for the active transport of antibiotics out of bacterial cells, thereby ensuring the maintenance of low intracellular concentrations (Figure 11). The phenomenon of bacterial multidrug resistance (MDR) can be attributed to a decrease in the permeability of the outer membrane (OM), which subsequently leads to a lower uptake of drugs. The investigation conducted in the postgenomic era has provided evidence of the presence of a significant number of multidrug efflux pumps in bacterial organisms. Additionally, the structural analysis of co-crystals of multidrug efflux pumps has provided insights into the mechanisms by which these pumps recognize and export drugs, as well as the methods by which they can be inhibited. The ability of a single multidrug efflux pump to transport several drugs underscores the importance of finding efflux pump inhibitors as a critical strategy in addressing infectious illnesses resulting from multidrug-resistant bacteria (Giedraitienė et al., 2011).

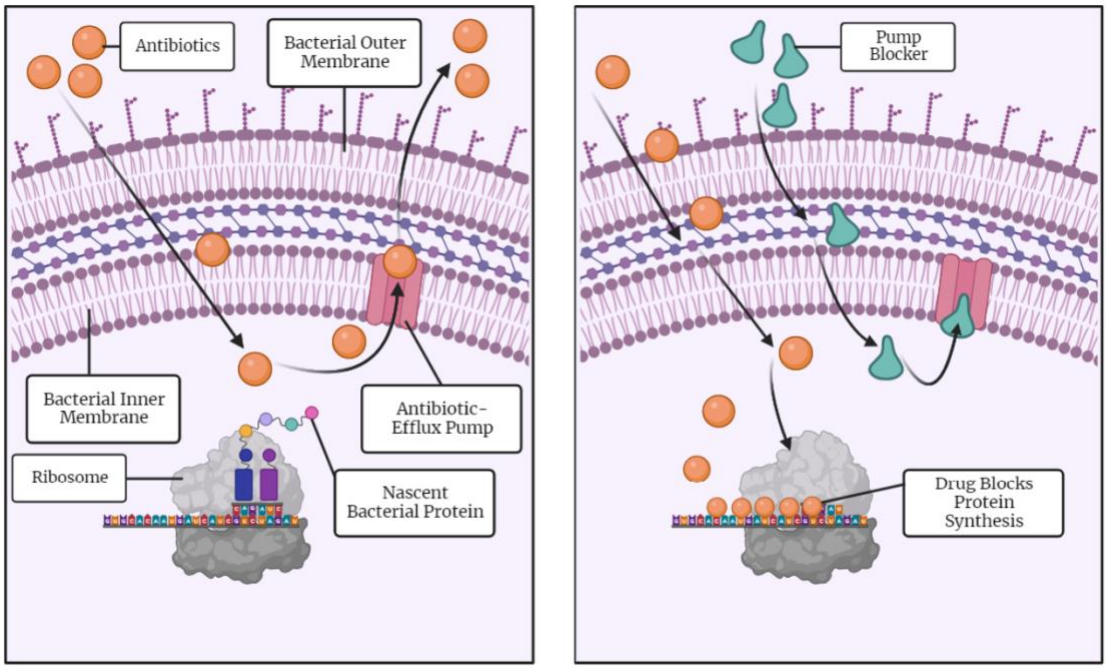


Figure 11: Multidrug efflux pumps refer to a class of inner membrane transporters that facilitate the exportation of several antibiotics from the intracellular environment to the extracellular space of bacterial cells. These pumps play a significant role in the development of bacterial multidrug resistance (MDR). The investigation conducted in the postgenomic era has provided evidence for the presence of a significant number of multidrug efflux pumps in bacterial organisms. Additionally, the structural analysis of co-crystals of multidrug efflux pumps has provided insights into the mechanisms by which these pumps recognize and export drugs, as well as the methods by which they can be inhibited. The exportation of numerous drugs can be facilitated by a single multidrug efflux pump. Therefore, the development of efflux pump inhibitors plays a key role in addressing infectious diseases that arise from bacteria with multidrug resistance. This review article elucidates the significance of multidrug efflux pumps in multidrug resistance (MDR), along with their physiological roles and inhibitory mechanisms.

6. Conclusion

Antimicrobial Resistance to sulfonamide, macrolides (such as azithromycin), penicillin, tetracycline, quinolones, and even ceftriaxone as a primary treatment option has been consistently observed in a substantial fraction of the gonococcal population for prolonged periods of time. In the event of the most severe outcome, gonorrhea has the potential to develop resistance to available treatments, rendering it untreatable.

Zoliflodacin a new class of antibacterial drugs known as spiropyrimidinetriones, is an orally accessible antibacterial drug with bactericidal activity against bacterial type II topoisomerases. DNA topoisomerases are enzymes in cells that regulate the three-dimensional structure of DNA inside DNA. Tigecycline, offers increased potency against a wide range of pathogens, including multidrug-resistant organisms. Upon entering the bacterial cell, tigecycline diffuses across the cytoplasmic membrane and reaches the ribosomes, which are responsible for protein synthesis and effectively inhibit the incorporation of new amino acids into the nascent polypeptide chain. Zoliflodacin, tigecycline, and ertapenem in single or dual therapy with ceftriaxone could be considered as a potential option for treating gonorrhea resistant to antibiotics. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gepotidacin is effective for GyrA A92T mutation in gonorrhea infection.

The phenomenon of bacterial multidrug resistance (MDR) can be attributed to a decrease in the permeability of the outer membrane (OM), which subsequently leads to a lower uptake of drugs. The investigation conducted in the postgenomic era has provided evidence of the presence of a significant number of multidrug efflux pumps in bacterial organisms.

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Identification of *Candida* Isolates from Cancer Patients Using Multiplex PCR

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Abstract
Aim of this study was to identify the *Candida* isolates from Cancer Hospital Maharagama, Sri Lanka by using Multiplex PCR (polymerase chain reaction) method. In this study, Multiplex PCR was used to identify *Candida* isolates from cancer patients at Apeksha Hospital, Sri Lanka. In multiplex PCR, 18 specific primers (nine primer pairs) were separated into three groups for multiplex PCR (PS I, PS II and PS III). Different sized PCR products corresponding to each *Candida* species were produced by PCR using the primer mixes. Among 52 *Candida* isolates, 49 were identified using the multiplex PCR procedure. *Candida tropicalis* was found to be the most prevalent species (38%), followed by *Candida parapsilosis* (31%), *Candida albicans* (13%), *Candida glabrata* (8%) and *Candida krusei* (4%). The study concludes that multiplex PCR is a better approach for the identification of *Candida* species and recommends the use of it for clinical and diagnostic purposes and for research purposes.

Keywords: Multiplex PCR, Cancer Patients, *Candida*

1. Introduction

Candida species are the most common opportunistic pathogens in debilitated or immunocompromised hosts and cause systemic candidiasis, which has high rates of morbidity and mortality. Immunocompromised individuals, such as those getting chemotherapeutic treatment for cancer are susceptible to a multitude of life-threatening opportunistic infections caused by *Candida* (Chi-Yang Lin et al., 2007). In recent years antifungal drug resistance of *Candida* species has become a major problem in the effective management of cancer patients in Sri Lanka. Identification of drug-resistant *Candida* strains has become an important supporting tool for physicians faced with making difficult decisions regarding treatment of patient with *Candida* infection. The first step in effective antifungal treatment is the identification of the pathogenic *Candida* species. Identification methods could be of various forms, such as molecular biochemical or morphological.

In earlier investigations on the epidemiology of *Candida* sp. various phenotypic characteristics were utilized to determine, but the methods lacked resolving capacity and were also frequently erroneous and time-consuming.

With the advent of molecular genetics, new, more powerful DNA-based typing methods have emerged as the "gold standard" for epidemiological studies.

Multiplex PCR is a rapid diagnostic test that mixes primers from numerous distinct species in a single PCR tube. Consequently, it might be used to concurrently identify multiple species in a specimen (Mahmoudi Rad et al., 2012). But when using Multiplex PCR, it is critical to design and use accurate primers according to the study that conduct.

In Sri Lanka, any reports of using multiplex PCR on identification of *Candida* species have not been published up to date so this study will be helpful to establish a proper molecular identification facility in Apeksha Hospital, Sri Lanka.

The study aims to investigate the molecular identification of *Candida* isolates through multiplex PCR. The first objective is to utilize multiplex PCR for the molecular identification of *Candida* isolates. Secondly, the study aims to evaluate effectiveness of this method in identifying *Candida* species. By achieving these objectives, the study seeks to contribute to the understanding of *Candida* species distribution and improve diagnostic approaches for identifying *Candida* in cancer healthcare settings.

2. Methodology

2.1 Sample Collection

Candida isolates were collected from the Microbiology laboratory of the Apeksha Hospital Maharagama Sri Lanka. The original samples were cultured in a blood agar medium, and for experimental purposes, they were again sub-cultured in Sabouraud Dextrose Agar medium and Sabouraud Dextrose Broth medium.

2.2 DNA Extraction

DNA was extracted using the Qiagen DNeasy Blood and Tissue Extraction Kit (Quiagen India 2019).

2.3 Multiplex PCR of DNA samples

Nine primer pairs specific to *Candida* species (Table 2) were categorized into three Primer mixes. (Ps I, Ps II and Ps III (Table 3)) to use in multiplex PCR. Initially all the DNA samples extracted from *Candida* isolates were amplified using the primers in Ps I group and visualized. The DNA samples that tested negative to the primers in Ps I was subjected to amplification using Ps II primers. The remaining DNA samples that tested negative to both Ps I and Ps II were amplified using the primers in Ps III.

DNA samples were amplified in 50 µL reactions containing 10 µL genomic DNA (10–30 µg/mL), 10 µL 10× PCR buffer, 5 µL $MgCl_2$ (25mM), 2.5 µL dNTPs (10 mM), 1.5 µL forward primer (100 pmol/uL), 1.5 µL reverse primer (100 pmol/uL) (total volume of the all forward and reverse primers varies from mix to mix.) with and 1 µL *Taq* DNA polymerase (5 units /µL) (Kanbe *et al*., 2002).

Final volume was adjusted to 50 µL using PCR grade water depending on the total volume of respective primer set.

The PCR was performed, preheating at 96 °C for three min, then 30 cycles of 90 °C for 45 s, 55 °C for 30 s, 72 °C for 90 s with final extension for 10 min at 72 °C.

Table 2: Primers used in this study for PCR amplification and their oligonucleotide sequences. (Kanbe et al., 2002)

Target species	Primer	Direction (F/R)	Sequence
C. albicans	CABF59	F	5'-TTGAACATCTCCAGTTTCAAAGGT-3'
	CADBR125	R	5'-GTTGGCGTTGGCAATAGCTCTG-3'
C. parapsilosis I	CPPIF41	F	5'-TGACAATATGACAAAGGTTGGTA-3'
	CPPIIR122	R	5'-TGTCAAGATCAACGTACATTTAGT-3'
C. parapsilosis II	CPPIIF41	F	5'-GGACAACATGACAAAAGTCGGCA-3'
	CPPIIR69	R	5' -TTGTGGTGTAATTCTTGGGAG-3'
C. dubliniensis	CDBF28	F	5'-AAATGGGTTTGGTGCCAAATTA-3'
	CDBR110	R	5'-GTTGGCATTGGCAATAGCTCTA-3'
C. krusiei	CKSF35	F	5'-GAGCCACGGTAAAGAATACACA-3'
	CKSR57	R	5' -TTTAAAGTGACCCGGATACC-3'
C. kefyr	CKFF35	F	5' -CTTCCAAAGGTCAGAAGTATGTCC-3'
	CKFR85	R	5'-CTTCAAACGGTCTGAAACCT-3'
C. glabrata	CGBF35	F	5' -CCCAAAAATGGCCGTAAGTATG-3'
	CGBR103	R	5' -ATAGTCGCTACTAATATCACACC-3'
C. tropicalis I	CTPIF36	F	5' -GTTGTACAAGCAGACATGGACTG-3'
	CTPIR68	R	5' -CAAGGTGCCGTCTTCGGCTAAT-3'
C. tropicalis II	CTPIIF36	F	5' -CTGGGAAATTATATAAGCAAGTT-3'
	CTPIIR121	R	5' -TCAATGTACAATTATGACCGAGTT-3'

Table 3: Primer mixes and specific primers in each of the mixes (Kanbe et al., 2002)

Primer Mix	Target species	Forward primer	Reverse primer	Size of the PCR product (bp)
Ps I	*C. albicans*	CABF59	CADBR125	665
	C. parapsilosis I	CPPIF41	CPPIR122	837
	C. parapsilosis II	CPPIIF41	CPPIIR69	310
Ps II	*C. dubliniensis*	CDBF28	CDBR110	816
	C. krusei	CKSF35	CKSR57	227
	C. kefyr	CKFF35	CKFR85	532
	C. glabrata	CGBF35	CGBR103	674
Ps III	*C. tropicalis I*	CTPIF36	CTPIR68	318
	C. tropicalis II	CTPIIF36	CTPIIR121	860

2.4 Visualization of PCR products

All PCR products were visualized by running gel electrophoresis at 100 V for 30 min, using 0.8% agarose gels stained with ethidium bromide, under UV light. The gels were photographed using the BioRad GelDoc system.

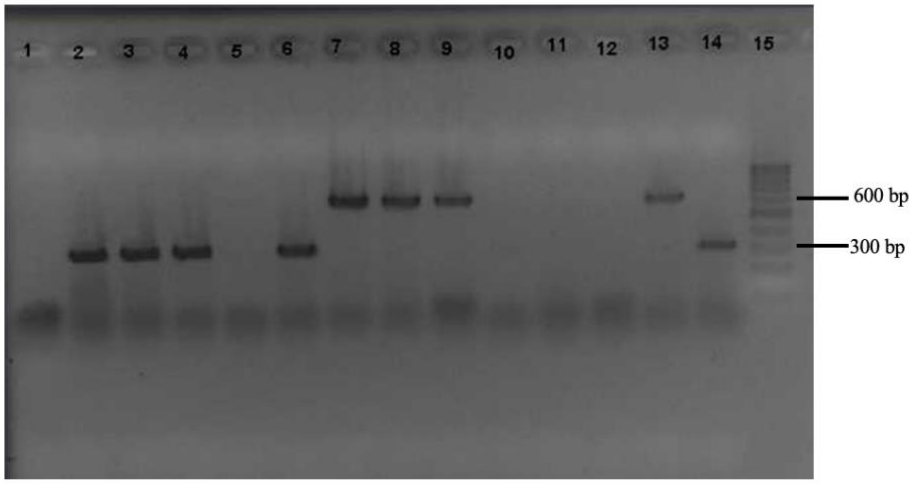
3. Results

Out of the 52 *Candida* isolates,49 isolates were identified using the multiplex PCR procedure.

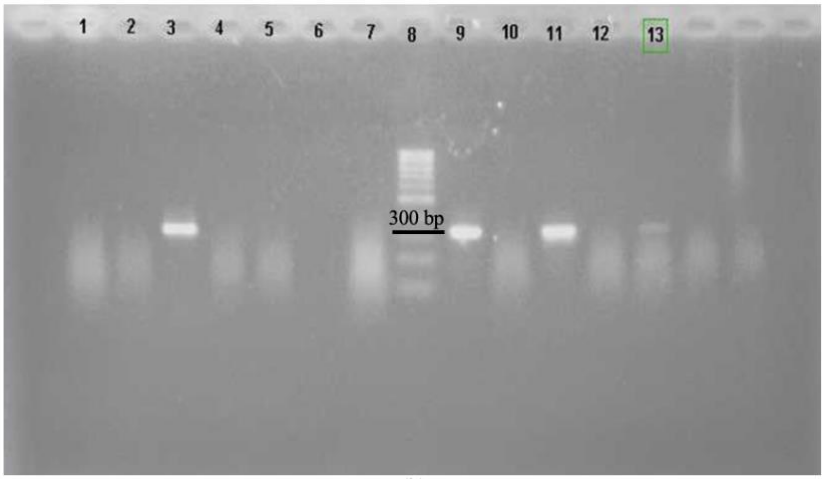
Out of 49 *Candida* isolates 20 were *C. tropicalis II* (38%), followed by 16 *C. parapsilosis* II (31%), seven *C. albicans* (13%), four *C. glabrata* (8% and two *C. krusei* (4%).

C. tropicalis strains I / II and *C. parapsilosis* strains I / II can be differentiated using multiplex PCR primers that used in this study. Out of 52 samples all 20 *C. tropicalis* samples were identified as *C. tropicalis II (*38%) and all

16 *C. parapsilosis* samples were identified as *C. parapsilosis II* (31%) and *C. tropicalis* I and *C. parapsilosis* I were not recorded.



(a)

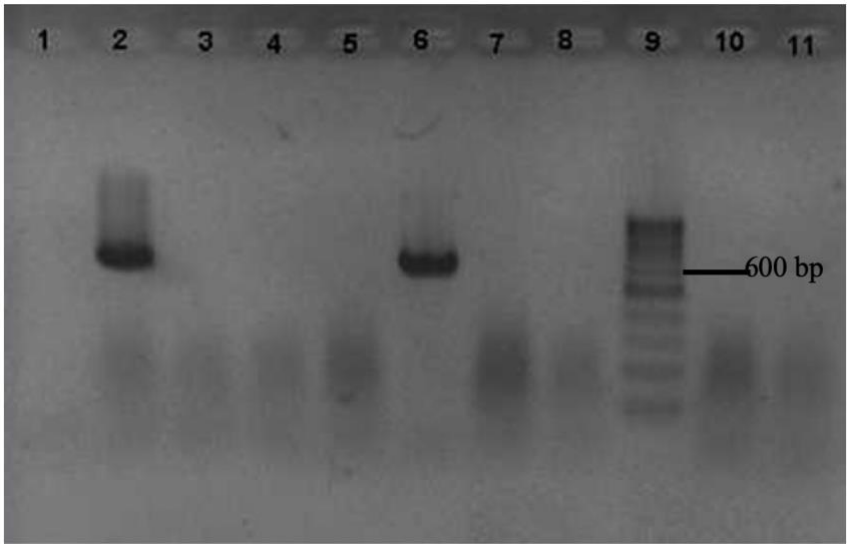


(b)

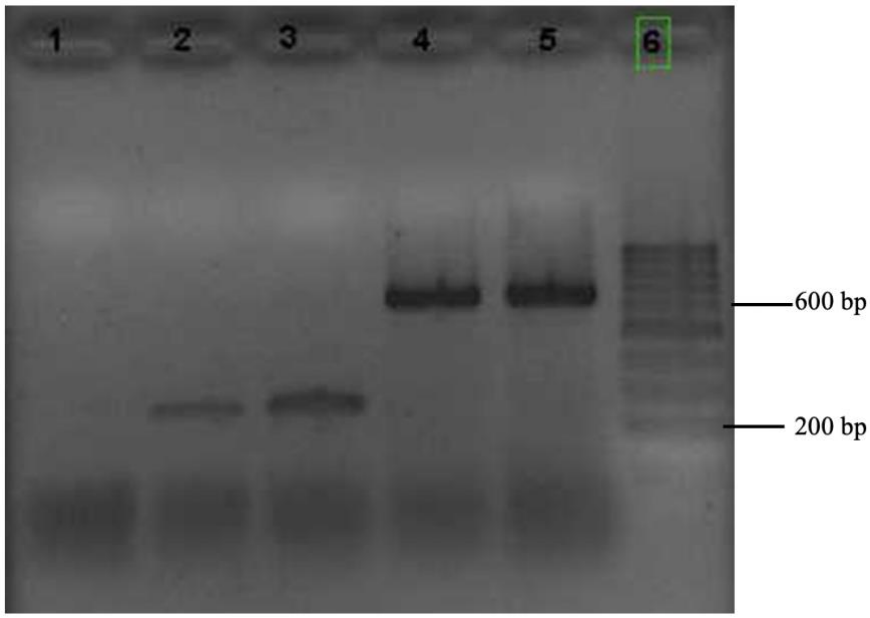
Figure 1: Multiplex PCR products of *Candida* isolates with the Ps I primer mix separated on 0.8% agarose gel.

(a) Lane 1: negative control; lane 2,3,4,6,14: *C. parapsilosis II*; lanes 7,8,9,13: *C. albicans*; lane 15: Molecular marker.

(b) Lane 1 and 2: negative control; lane 3,9,11: *C. parapsilosis II*



(a)



(b)

Figure 2: Multiplex PCR products for the Ps II primer mix separated on 0.8% agarose gel

(a) Lane 1: negative control; lane 2 and 6: *C. glabrata*; lane 9: Molecular marker.

(b) Lane 1: negative control; lane 2 and 3: *C. krusei*; lane 4 and 5: *C. galbrata* ; Lane 6 : Molecular marker.

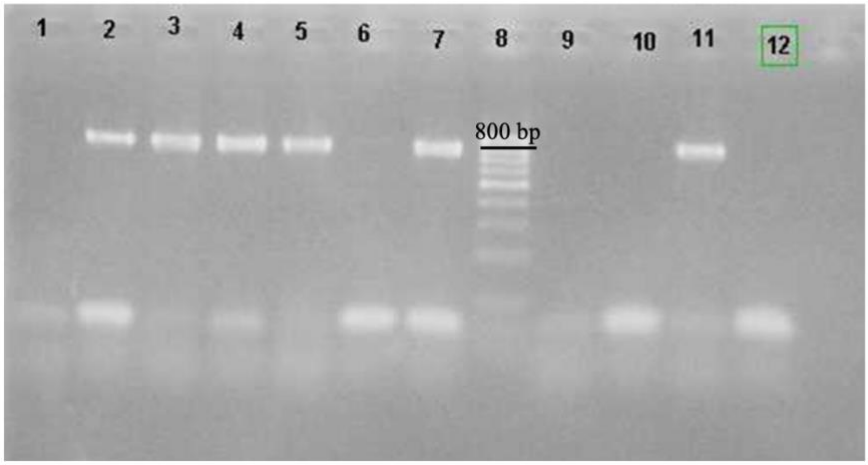


Figure 3: Multiplex PCR products for the Ps III primer mix separated on 0.8% agarose gel.
Lane 1: negative control; lanes 2,3,4,5,7 and 11: *C. tropicalis II*; Lane 8: Molecular marker.

4. Discussion

Candida infections have increased significantly in recent years which may be due to the aggressive use of immunosuppressants among patients such as cancer patients. Rapid and accurate *Candida* identification plays a critical role in effective management of *Candida* infections.

The DNA topoisomerase II gene is present in all eukaryotes, and its nucleotide sequence is composed of highly conserved regions separated by species-specific regions. The sequence analysis of the DNA topoisomerase II (DNA gyrase) gene was applied not only to understand phylogenetic relationships but also for development of a diagnostic identification system of broad species of medically important microorganisms by PCR (Huang, 1996). Based on the characteristics of the *Candida* DNA topoisomerase II genes, Kato *et al*., 2001 suggested that they were suitable as targets for PCR based identification of several *Candida* species. This study used previously designed specific primers by Kato *et al*., 2001 to the DNA topoisomerase II genes of *Candida* species by using Multiplex PCR.

49 isolates out of 52 (87.03%) were identified using the multiplex PCR procedure. The Multiplex PCR analysis provided further insights into the specific strains within *C. tropicalis* and *C. parapsilosis*, distinguishing between strain I and strain II. This level of strain identification can have implications for understanding strain-related virulence factors, genetic diversity, and potential differences in antifungal resistance profiles. According to Arastehfar *et al*., 2018 multiplex PCR procedure is one of the most accurate methods to identify *Candida* species. However, for the multiplex PCR procedure, species-specific primers are required. This process could be expensive, and the primer sets should be customized according to the species estimated to be identified.

In this study *C. tropicalis* was the most prominent species, constituting 38% of the isolates. This finding suggests that *C. tropicalis* infections may be more prevalent in the studied population. This finding aligns with some previously conducted research studies. According to Kumar, *2018 C. tropicalis* has also emerged as an important opportunistic fungal pathogen. That study concludes that incidents of *C. tropicalis* infections have risen all over the world in past two decades.

C. parapsilosis was the second most prominent species, accounting for 31% of the isolates. This finding aligns with previous research indicating that *C. parapsilosis* is a significant cause of candidemia and other infections, particularly in healthcare settings. According to Trofa et al., 2008., *Candida parapsilosis* is an emerging major human pathogen that has dramatically increased in significance and prevalence.

In the past, *Candida albicans* was considered the most prevalent species causing *Candida* infections. However, according to some studies in recent years, there has been an increase in the prevalence of non-*albicans Candida*

species such as *C. tropicalis* and *C. parapsilosis*. In a study conducted by Deorukhkar et al., 2014, non-*albicans Candida* species were the predominant pathogens isolated. These findings are like this study because, during the study period*, C. tropicalis* and *C. parapsilosis* were most prominent. A recent study conducted by Sigera et al., 2019 in Sri Lanka has also demonstrated that non albicans species are more prominent than *C. albicans* in Sri Lanka. Their finding on *C. tropicalis* and *C. parapsilosis* being the most prominent species agrees with the findings of this study.

Even though *C. glabrata and C. krusei* may not be as prevalent as C. tropicalis or C. parapsilosis, these species have been known to cause infections with unique characteristics and varying antifungal susceptibility patterns. Further investigation is warranted to understand the specific risk factors and clinical implications associated with these less common *Candida* species.

This study employed multiplex PCR techniques to identify *Candida isolates*. However, to further enhance the accuracy and resolution of results, future investigations can incorporate sequencing methods.

Multiplex PCR offers a higher level of resolution by differentiating specific strains within the identified *Candida* species. And Multiplex PCR is one of the most accurate methods to identify *Candida* species. Researchers interested in understanding the molecular epidemiology of *Candida* infections or investigating specific strain characteristics may find Multiplex PCR to be a more suitable choice (Arastehfar *et al*., 2018).

Multiplex PCR, with its ability to differentiate species and specific strains within identified species, is more valuable for research purposes (such as studying genetic diversity, strain-related characteristics, and molecular epidemiology) and in clinical diagnosis.

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Management of Respiratory Failure in Peripartum Cardiomyopathy Patient: Case Report

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Abstract
Introduction: Respiratory failure in peripartum cardiomyopathy is a lethal risk. The onset of respiratory failure in peripartum cardiomyopathy is due to left-to-right heart failure, which lowers PaO2. Unfortunately, symptoms of peripartum cardiomyopathy are often non-specific and progressive, so diagnosis and treatment are frequently delayed. Case: A woman, 41 years old, 35-36 weeks pregnant, complains of shortness of breath for four days, worsening one day before hospitalization. Cough (-), The patient has no history of heart disease; this is her 5th pregnancy, and she has never complained of the same thing in previous pregnancies. physical examination of consciousness, compost mentis,BP 90/60 mmHg, HR 122 x/i, RR 32-36 x/I, T 36.5 °C,, Spo2 is 85% without O2. On examination, blood gas analysis showed a respiratory alkalosis with type 1 respiratory failure. The patient underwent an emergency cesarean section on the indication of type 1 respiratory failure—postoperative care in the ICU with the installation of a ventilator. During the five days of treatment, the patient's condition improved when transferred to the ward. Discussion: Respiratory failure in peripartum cardiomyopathy results from a low PaO2, usually accompanied by an accumulation of fluid in the interstitial lung tissue (pulmonary edema), which exacerbates hypoxaemic conditions due to decreased cardiac output. Airway protection is significant, such as performing mechanical ventilation with sedation to optimize oxygen delivery; giving inotropic (digoxin) and vasoactive drugs (dopamine or dobutamine) to increase contractility and maintain mean arterial pressure (MAP) for organ perfusion; reducing preload and afterload; and maintaining negative fluid balance while paying attention to adequate organ perfusion. Conclusion: Airway patency is the primary key in the management of respiratory failure in patients with peripartum cardiomyopathy

Keywords: Respiratory Failure in Pregnancy, Peripartum Cardiomyopathy, Intensive Care Unit

1. Introduction

Peripartum cardiomyopathy, also known as peripartum cardiomyopathy (PPCM), is a rare idiopathic cardiomyopathy that develops without a known cause in the last month of pregnancy or the first six months after delivery. PPCM can only be diagnosed by exclusion, as there is no agreement on diagnostic standards.t(Ng et al., 2022). Complications of cardiovascular disease accompany approximately 0.2 - 4% of pregnancies in developed

countries. (Regitz-Zagrosek et al., 2018). PPCM is a lethal condition with a reported average incidence of between 1/3000 and 1/4000, accounting for about 4% of maternal deaths (Ng et al., 2022; Regitz-Zagrosek et al., 2018). On echocardiographic examination, there will be a decrease in the left ventricular systolic function below 45%, accompanied by symptoms of cardiac decompensation that arise during labor without any evidence of a previous history of heart disease.(Kawamoto et al., 2021; Minami et al., 2018).

Clinical manifestations of PPCM consist of dyspnea, cough, and hypertension. They can be followed by severe heart failure within hours to days. Therefore, early diagnosis concerning the airway is essential for PPCM patients with respiratory failure due to effective treatment with ventilation reducing morbidity and mortality. For this reason, this case report is peripartum cardiomyopathy with respiratory failure (Dahiya et al., 2020; Johnson-Coyle et al., 2012; Minami et al., 2018).

2. Case report

A multigravida woman with a gestational age of 35-36 weeks complained of shortness of breath for four days and worsened one day of SMRS. Shortness of breath initially occurs when the patient walks to the bathroom, but the shortness of breath goes away with rest. The patient admits that she began to feel shortness of breath when lying down at six months of gestation, which reduced if the patient used 3-4 pillows. However, since one day of SMRS, the tightness has worsened and doesn't go away with rest. The patient claimed to have no complaints such as cough, fever, or complaints like this in previous pregnancies. This is the 5th pregnancy for the patient, history of abortion (-). The patient had no previous history of heart disease or lung disease. On examination, the consciousness was compos mentis, BP 90/60 mmHg, HR 122 x/i, RR 32 – 36 x/i, T : 36.5°C, SpO2 : 85% without O2. Physical examination showed TVJ increased 5 ± 4 cmH20. On auscultation of the lungs, wet basal crackles were seen accompanied by gallop sounds (+). The patient also underwent a chest X-ray examination for cardiomegaly with pulmonary edema. On echocardiographic examination, an EF of 35% and left ventricular dilatation were seen (Figure 2). Laboratory examination found no abnormalities, and blood gas analysis showed respiratory alkalosis with type 1 respiratory failure (pH: 7.51 mmHg, PO2: 44 mmHg, PCO2: 25 mmHg, HCO3: 22, BE: -1.7, SaO2: 91.8 %). The patient was given 100 mg of furosemide followed by 60 mg with monitoring of urine output (UOP), drip dobutamine five mcg/kilogram body weight/minutes, and injection of enoxaparin 1 x 0.6 cc. An emergency cesarean section (SC) was performed under general anesthesia. The operation lasted 15 minutes with a urine output of 1000 ml and bleeding of 400 ml. Furthermore, the patient was treated in the ICU with the installation of a ventilator with RR 20, PEEP 8, I; E = 1:2, FiO2 50%, SpO2: 97-98%. On day four, the patient's condition improved with CM awareness, BP: 120/80 mmHg, HR: 88 x/minutes RR: 24 x/minutes, temperature: 36.7 C, SpO2: 98% with O2 liters per minute nasal cannula. On day 5, the patient was transferred to the ward.

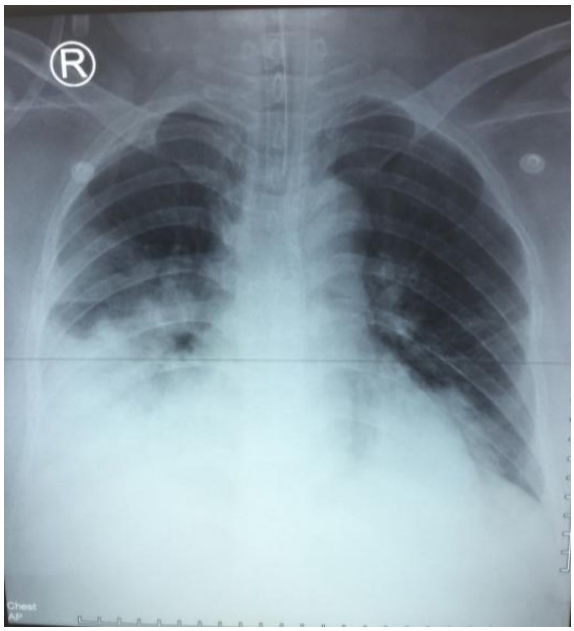

Figure 1: Photo of the PPCM Chest

Figure 2: PPCM echocardiography

3. Discussion

During a typical pregnancy, 60% to 70% of pregnant women report having difficulty breathing. Physicians should be aware of PPCM because it can easily be misdiagnosed due to vague symptoms. The true prevalence of PPCM is unknown. The incidence ranges from 1 in 1300 to 1 in 15000 pregnancies Morbidity and mortality ranges from 25% to 90% due to geographic and diagnostic variation (Çimen et al., 2013). Usually, the PPCM condition is often accompanied by pulmonary edema on chest X-ray examination, which is also found in this patient. PPCM deaths generally result from heart failure, pulmonary embolism, and respiratory failure. Therefore, early management is crucial to prevent mortality in patients with PPCM.

Pulmonary edema occurs in PPCM patients due to heart failure and causes respiratory failure. The process of pulmonary edema in PPCM patients due to heart failure in the systolic and diastolic phases. Systolic heart failure is characterized by weakened left ventricular contractions that occur, while diastolic heart failure is characterized by the inability to dilate at the time of filling of the left ventricle resulting in decreased cardiac output. Compensatory mechanisms for decreased cardiac output are characterized by vasoconstriction and fluid retention. Vasoconstriction arises as a result of the resulting hypoxia, which stimulates the release of noradrenaline. In addition, decreased blood supply to the kidneys stimulates the renin-angiotensin system, which causes systemic vasoconstriction. In the short term, all of these mechanisms increase cardiac output. Compensatory vasoconstriction can lead to increased cardiac output but can weaken cardiac function. Furthermore, the increased pressure and volume in the left ventricle will eventually increase the pressure and importance in the pulmonary

circulation, which causes the movement of intravascular fluid into the alveolar cells and interstitial space. g(Andre et al., 2022; Shebl et al, 2022)

The mechanism of hypoxia arises in PPCM patients due to decreased oxygen delivery (DO2). Oxygen delivery levels depend on cardiac output (CO) and oxygen content of the arterial blood (CaO2). In patients with PPCM cardiac output has decreased so that compensation occurs with vasoconstriction and fluid retention, which increases afterload. The increased afterload on the left ventricle causes pulmonary congestion, which reduces the diffusing capacity of the lung, causing an increase in intrapulmonary shunt resulting in arterial hypoxemia. Another mechanism is pump failure, which causes decreased cardiac output and reduced tissue perfusion leading to circulatory hypoxia (Ramachandran et al., 2022).

Management of peripartum cardiomyopathy is mainly supportive. Where medical therapy for peripartum cardiomyopathy is the same as for heart failure, the management must involve a medical team consisting of cardiologists, obstetricians, and anesthesiologists to achieve optimal results during pregnancy and childbirth. In administering therapy, besides attaining optimal results for the mother, the effects of the drug on the fetus and baby who are breastfeeding must also be considered. The goal of therapy in patients with peripartum cardiomyopathy is hemodynamic optimization, optimizing preload, reducing afterload, and increasing contractility. Standard treatment in peripartum cardiomyopathy is: bed rest, and oxygenation, to maintain tissue oxygenation to help prevent end-organ dysfunction and multiple-organ failure (Lata et al., 2009; Shaikh, 2010).

Treatment of PPCM is based on improving the patient's hemodynamic status by reducing preload and afterload and increasing the heart's contractile strength, as in the treatment of heart failure. Management of acute decompensated heart failure still pays attention to the airway, breathing, and circulation. The airway must be secured as early as possible because the accumulation of interstitial fluid can result in airway edema and exacerbate hypoxemia due to decreased cardiac output. Patients with pulmonary edema often require assisted ventilation. In addition, the target for arterial oxygen saturation ≥ 95% should be achieved. Interventions can be performed, such as performing mechanical ventilation with sedation to optimize oxygen delivery, giving inotropic and vasoactive drugs to increase contractility and maintain mean arterial pressure (MAP) for organ perfusion, reducing preload and afterload and maintaining negative fluid balance while paying attention to the adequacy of organ perfusion (Dash et al., 2022; *Fragneto R,* 2006; Shaikh, 2010).

Safe inotropic drugs for pregnant and lactating women, namely digoxin, increase the ejection fraction in combination with a vasodilator. Usually, administration for 6-12 months reduces the risk of PPCM recurrence. In addition to inotropes, the administration of vasoactive drugs such as dopamine or dobutamine can be considered. For this reason, it is essential to know PPCM early and immediately administer therapy to reduce the morbidity and mortality of PPCM sufferers (Dash et al., 2022).

4. Conclusion

PPCM is a condition rarely found in pregnant women and is usually characterized by shortness of breath that appears at the last gestational age up to 6 months after giving birth. PPCM conditions often need to be explained. Therefore it is essential to consider PPCM in pregnant women who complain of severe shortness of breath in late pregnancy or up to 6 months postpartum. PPCM mortality is very high if it is late in diagnosis and therapy. Therefore airway patency is the primary key to managing respiratory failure in patients with cardiomyopathy.

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Systematic Review in Population-Based General Understanding Surveys of Stroke Perception, Potential Risks, Treatments, and Perspectives for a Correlative Study on Public Awareness Between Different Age Groups and their Lifestyles

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Abstract
Background: Stroke is a major public health concern that may affect a patient's physical performance and ability to perform fundamental daily duties. Understanding the fundamentals of stroke is crucial for lowering mortality and disability rates among patients, as it allows for the preparation of a rapid and effective treatment and the comprehension of the therapy and treatment process following a stroke. Methods: A survey was distributed to 122 individuals, including 24.6% of high school pupils (12-17), 25.4% of young adults (18-25), 16.4% of adults (26-40), and 33.6% of middle-aged adults (41-60). After completion of data gathering, descriptive analysis was carried out. Results: the outcomes revealed that most participants scored higher on the general comprehension questionnaires than on the technical section. Notably, the level of comprehension of middle-aged adults ($x = 9.50$) appeared to be the highest. Moreover, those with direct experience with stroke or direct contact with stroke patients had a greater understanding of the disease and its treatment ($x = 9.05$, $p = 0.08$) than those without such experience/contact ($x = 8.00$, $p = 0.08$). Nevertheless, according to statistical analysis, there was a positive correlation between the age range of participants and their disease awareness. However, the self-care conducted was mostly found in adolescence. Discussion: Therefore, it is necessary for government organizations to encourage awareness and education about fundamental treatments that can assist individuals in avoiding possible risk factors by implementing the FAST guideline simultaneously with a public education effort on stroke response. The greater the number of individuals who comprehend the method for coping with the disease, the greater their protection against the disease.

Keywords: Stroke, Public Awareness, FAST Guideline, Stroke Knowledge Levels, Lifestyles, Age Groups

1. Introduction

1.1 Introduce the Problem

Stroke is currently a significant public health issue. This disease is the third-leading cause of mortality and disability in the world (Feigin et al., 2021). In addition, experiencing a stroke might result in adverse consequences and complications among the patients, for instance, paralysis on one side of the body or the hemiplegia, muscle spasms (Cauraugh et al., 2003) and aphasia, communication impairment (Pedersen et al.,1995). Symptoms of a stroke diminish a patient's physical performance and ability to conduct basic daily tasks. It can also have an impact on psychological, emotional, and behavioral variability (Brice et al., 2002; Chemerinski et al., 2000; Paul et al.,2013). As a result of its effect on the patient's brain, it can cause aggression (Kim et al., 2002) as well as limitations in comprehension abilities (Pinkston et al., 2009).

1.2 Importance of the Problem

Understanding the fundamentals of stroke becomes essential for reducing deaths and the disability rate among patients. This will allow individuals who may be struggling to cope with the initial symptoms that may manifest in emergency circumstances. In prefer to be able to prepare for a fast and effective treatment (Brice et al., 2002; Skolarus et al., 2013) and to comprehend the therapy and treatment process following a stroke in a systematic way. It might additionally have an influence on raising awareness of these diseases (Fogle et al., 2008) such that individuals can take care of themselves by avoiding various risk factors that may contribute to the disease. Along with getting diagnoses and regularly looking after themselves (Das et al., 2013).

Therefore, the research aims to investigate the public understanding of stroke disease in terms of the sign and symptom, its diagnosis, and treatments. Along with this, the study intends to examine the exhibited of statistical correlation between the participants 'demographic and their level of the disease knowledge with the comparison on the comprehension in different groups of age; adolescents (12-17), young adults (18-25), adults (26-40) and middle-aged adults (41-60). Yet, the study also examines the correlation between the age range of those taking part and their public awareness and self-care conducted regarding the disease.

1.3 Literature review

1.3.1 Stroke disease

Stroke, also known as cerebrovascular accidents (CVA), is the neurological manifestation of a severe reduction of cerebral blood flow in a circumscribed region of the brain, caused by the abrupt or progressively progressing occlusion of a large brain artery (Hossmann et al., 2006), which can be brought on by a variety of risk factors, medical conditions, and body mechanisms. In addition, ischemic strokes, which make up for approximately 85 percent of all strokes, are caused primarily by cerebral small vessel disease, cardiac embolism, and atherosclerosis-related thrombosis in large arteries, and approximately 15 percent of strokes are caused by intracerebral hemorrhage, which can occur in deep regions of the brain (Murphy et al., 2020). Furthermore, the most typical presenting signs and symptoms of ischemic stroke include hemiparesis and speech difficulty (Yew et al., 2009).

1.3.2 FAST guideline

The FAST acronym is widely used for stroke public education, which was designed in 1999 for easier mnemonics on the potential symptoms and for initial assessment for obtaining emergency healthcare. Face, Arm, Speech, and

Time are represented by each letter, respectively. To exemplify more, the letter "F" was used to determine numbness or dropping of the face, followed by the letter "A" which meant to check for arm weakness, particularly on one side of the patient's body. Then, the "S" for indication of comprehension and speech difficulty Lastly, is to emphasize the patient's need to get immediate treatment by calling 911 is represented by the letter "T." In terms of effectiveness, it is readily apparent that it is a better identification method for ischemic stroke and transient ischemic attack (TIA) than for hemorrhagic stroke. Consequently, about 88.9% of stroke/TIA patients were determined as a result of the use of this message (Kleindorfer et al., 2007)

1.3.3 Diagnoses and Treatments

The standard diagnostic evaluation for patients with a suspected stroke consists of a thorough medical history and physical checkup, as well as a neurologic examination (Alberts et al.,1999). The American Heart Association's published guidelines emphasize the significance of a precise diagnosis and appropriate management among people presenting with stroke symptoms by suggesting individuals suspected of having a stroke undergo a brain imaging study to differentiate the types of strokes (Adams et al., 1994). Head computed tomography (CT) and brain magnetic resonance imaging (MRI) are the two standard neuroimaging procedures used to diagnose a stroke (Alberts et al.,1999). Moreover, there is a study that illustrates that the identification of potentially treatable cerebrovascular abnormalities in younger people with ischemic stroke is dependent on cerebral angiography (Ganesan et al.,1999).

Acute ischemic stroke offers a serious health risk because there are few effective therapies available, with the exception of thrombolytic recombinant tissue plasminogen activator (rt-PA). However, rt-PA must be administered within three hours of the onset of stroke symptoms due to its sensitivity to time (Green et al., 2006). To emphasize, the treatments for the stroke were mainly aimed at preventing other subsequent symptoms (Alberts et al.,1999).

1.3.4 General misconception

Previous studies reveal that there are still common beliefs that lead to misconceptions about stroke. These can be shown in Hsia et al. (2011) whose findings are conducted with underserved urban residents that aim to identify urban underserved population-specific misconceptions that may act as barriers to undergoing delayed treatments. The result of this suggested that nearly half of participants attributed the delay to the belief that the symptoms were not severe and/or would resolve themselves. Moreover, other studies that took place in African American under-resourced communities detailed the perception of the adult-aged participants, who figured that the disease always results in fatality, so seeking the medical profession would be superfluous (Skolarus et al., 2013). Furthermore, there is a study that demonstrates a misunderstanding about factors that can be a leading cause of stroke such as high blood pressure, heart disease, diabetes, and smoking. However, as hypertension, or high blood pressure, is considered one of the greatest risk factors, only 28.9% of the participants correctly identified it (Kaddumukasa et al., 2015).

1.3.5 Incidence of Stroke

The incidence of stroke is statistically higher globally and differs from region to region. According to studies, that detail the accordance with the WHO World Standard Population, the incidence of stroke in the studies went from 76 per 100,000 people per year in Australia (2009–10) to 119 per 100,000 people per year in New Zealand (2011–12), with the latter figure only applying to people who were at least 15 years old. Only in Martinique (2011–12) was the incidence of stroke higher among females than males. In countries without or with outdated data on stroke incidence, eight had national clinical hospital-based data registries. Kazakhstan, Bulgaria, and Greece had the highest absolute mortality rates among the 128 countries that reported mortality data to the WHO in 2003.

Although there was no relationship between time and crude mortality or crude incidence of stroke, both variables were positively linked with the percentage of those 65 years of age or older (Feigin et al. ,2013) .

1.3.6 Previous studies

In conditions characterized by a higher incidence of stroke, from the outset, however, the majority of patients and the general population still possess a misconception of the disease. Based on several previous studies, this is a crucial issue in understanding the basic concepts and techniques of stroke treatment in modern times. This evidence was shown in the four urban residential areas in China that assessed their public knowledge by providing semi-structured interviews and questionnaires to their non-stroke dwellers. The topics of contributing factors, medical therapy, symptoms, stroke education, emergency responses, and their main sources from which they received information about the diseases were identified in this study. The conclusion of this investigation was that urban individuals were still lacking stroke understanding. (Sun et al., 2011). Furthermore, referring to the Kothari et al. study, the general understanding of stroke survivors was investigated. Interestingly, it was found that nearly forty percent of patients admitted with a suspected stroke were unaware and had misunderstandings about the signs, symptoms, or risk factors associated with a stroke. (Kothari et al., 1997). Moreover, the results appeared to be the same as those shown in Hospital Raja Perempuan Zainab II, where a cross-sectional survey was conducted among stroke patients admitted to the medical and surgical wards. Within eight months, stroke patients were conveniently selected, and data were collected. The result showed that the patients themselves still had a lack of stroke knowledge, with 45% of respondents answering correctly on 9 items, while 35% had misconceptions regarding 7 items (35%). (Sowtali, et al., 2016). In addition, there was further research on the comparison between the terms "stroke patients" and "none of those," as it reveals in the Suvilan et al. study, which contains a stroke knowledge test conducted with 38 non-stroke survivors (community sample) and compared to the 42 stroke patients' data. Consequently, the outcomes suggested that there wasn’t a significant difference between the stroke survivors and their sample of non-stroke survivors (Sullivan, et al., 2005).

2. Methodology

A survey distributed to a total of 122 participants which included 24.6% of high school students, 25.4% of young adults, 16.4% of adults and 33.6% of middle-aged adults residing in Thailand via the online questionnaire for data acquisition in this study.

The question was designed into four main sections and was distinct between the participants in the group that had experienced/contacted the patients and the group that had no such experience/contacted. The assessment instrument consisted of a questionnaire with four sections, each of which focused on a distinct aspect of the respondent's understanding and their comprehension of the stroke medical condition and its treatments. In total, the questionnaire consisted of 20 questions.

The objective of the first section (5 questions) was to gauge the participants' general knowledge of the disease, its signs and symptoms, and its associated risk factors. The second section (5 questions) center on the participants' comprehension of the disease's available treatment options. The objective of the third section (5 questions) was to identify prevalent misunderstandings and erroneous assumptions regarding the disease. In the last component (5 questions), the 5-point Likert-type scales ranging from strongly disagree (scale 1) to strongly agree (scale 5) questions were used to determine participant preferences and opinions regarding the disease.

2.1 Recruitment

The recruitment of respondents was carried out using an internet-based survey procedure. Participants were approached through several channels of communication, including a variety of social media platforms, chat rooms, and intended community groups on the internet. The recruitment procedure included providing a brief overview of the study's contents investigation, the study's goals, consent, and a link to the online survey. Participants were encouraged to participate in the survey voluntarily and anonymously.

2.2 Data analysis

Following the conclusion of data collection, responses to the questionnaire were compiled and arranged for analysis. Descriptive analysis was conducted to calculate the participants' general knowledge levels for calculating the mean scores of the participants to indicate the overall level of comprehension about the disease and its treatments among the sample population. The statistical differences were also applied with the utilization of T-test analysis to identify the understanding in stroke disease among various age categories and to compare the comprehension of participants who had direct stroke experience with those who had not. Nevertheless, the relationship between comprehension and age was investigated through a correlation analysis to reveal the intensity and direction of the relationship, indicating whether understanding increased or decreased with age.

3. Results

3.1 Overall understanding

Based on the results of our analysis in Table A1, it can be concluded that the overall understanding of the diseases and treatments among the sample was moderate. However, upon further examination, there was no apparent correlation between the gender of the participants and their understanding. However, it was observed that the numerical data of the understanding in both genders did contain significant differences at the level of 71%, with the perception of females (x = 8.50) and males (x = 7.96).

Table A1: Descriptive Analysis of Female and Male Overall Understanding

	Female	*Male*
Mean	8.50151515	7.96363636
Standard Error	0.28876792	0.41894821
Median	8.45	7.6
Mode	7.3	9.3
Standard Deviation	2.34596166	3.10700306
Sample Variance	5.50353613	9.65346801
Kurtosis	-0.5749386	-1.0109194
Skewness	-0.1036104	0.17189504
Range	9.7	11.3
Minimum	3.3	3
Maximum	13	14.3
Sum	561.1	438
Count	66	55

Specifically, according to the statistical analysis in Table A2, most participants revealed that they were accounting for more points on the general understanding questionnaires compared to the technical tasks. The sample had a fair understanding of the general symptoms associated with stroke diseases, with an average score of 2.81 out of a possible 5. Additionally, their technical understanding of the diseases, including the number of signs, FAST guidelines, and diagnosis remedies, was deemed adequate, with an average score of 1.96 out of a possible 5.

Table A2: Descriptive Analysis of Technical and General Understanding

	Technical	*General*
Mean	1.96179775	2.80898876
Standard Error	0.11642997	0.13547895
Median	2	3
Mode	1.3	3
Standard Deviation	1.09839817	1.27810588
Sample Variance	1.20647855	1.63355465
Kurtosis	-0.7065659	-0.4613023
Skewness	0.19364439	-0.2004679
Range	4.3	5
Minimum	0	0
Maximum	4.3	5
Sum	174.6	250
Count	89	89

3.2 Ages and understanding

The correlation between age and comprehension was found to be statistically significant. The results indicate that the level of comprehension tended to improve as the age of the sample population increased. However, upon conducting a t-test analysis, it was determined that there were simply not any statistically significant distinctions in the level of understanding among adolescents (x = 7.34), young adults (x = 7.40), and adults (x = 8.51). Notably, the level of understanding of middle-aged adults (x = 9.50) appeared to be overwhelmingly the highest score compared to those age ranges: adolescents (x = 7.34, p = 0.00), young adults (x = 7.40, p = 0.00), and adults (x = 8.51, p = 0.10) (Seen in Table B1, Table B2, Table B3, Table B4, Table B5, Table B6).

Table B1: t-Test: Adolescents and Young Adults Understanding

	Adolescents	*Young adults*
Mean	7.34	7.4
Variance	6.32386207	5.754
Observations	30	31
Hypothesized Mean Difference	0	
df	59	
t Stat	-0.0952971	
P(T<=t) one-tail	0.46220087	
t Critical one-tail	1.67109303	
P(T<=t) two-tail	0.92440175	
t Critical two-tail	2.00099538	

Table B2: t-Test: Adolescents and Adults Understanding

	Adolescents	*Adults*
Mean	7.34	8.51
Variance	6.32386207	8.582
Observations	30	20
Hypothesized Mean Difference	0	
df	36	
t Stat	-1.4626195	
P(T<=t) one-tail	0.07612385	
t Critical one-tail	1.68829771	
P(T<=t) two-tail	0.1522477	
t Critical two-tail	2.028094	

Table B3: t-Test: Adolescents and Middle-aged Understanding

	Adolescents	*Middle-aged*
Mean	7.34	9.50243902
Variance	6.32386207	5.1232439
Observations	30	41
Hypothesized Mean Difference	0	
df	59	
t Stat	-3.7319361	
P(T<=t) one-tail	0.00021467	
t Critical one-tail	1.67109303	
P(T<=t) two-tail	0.00042933	
t Critical two-tail	2.00099538	

Table B4: t-Test: Young Adults and Adults Understanding

	Young adults	*Adults*
Mean	7.4	8.51
Variance	5.754	8.582
Observations	31	20
Hypothesized Mean Difference	0	
df	35	
t Stat	-1.4157508	
P(T<=t) one-tail	0.08284312	
t Critical one-tail	1.68957246	
P(T<=t) two-tail	0.16568624	
t Critical two-tail	2.03010793	

Table B5: t-Test: Young Adults and Middle-aged Understanding

	Young adults	*Middle-aged*
Mean	7.4	9.50243902
Variance	5.754	5.1232439

Observations	31	41
Hypothesized Mean Difference	0	
df	63	
t Stat	-3.7726247	
P(T<=t) one-tail	0.00017966	
t Critical one-tail	1.66940222	
P(T<=t) two-tail	0.00035933	
t Critical two-tail	1.99834054	

Table B6: t-Test: Adults and Middle-aged Understanding

	Adults	*Middle-aged*
Mean	8.51	9.50243902
Variance	8.582	5.1232439
Observations	20	41
Hypothesized Mean Difference	0	
df	30	
t Stat	-1.3332959	
P(T<=t) one-tail	0.0962356	
t Critical one-tail	1.69726089	
P(T<=t) two-tail	0.1924712	
t Critical two-tail	2.04227246	

3.3 Contacted and non-contacted stroke patients

Those with direct experience with stroke or direct contact with stroke patients had a greater comprehension of the disease and its treatment (x = 9.05, p = 0.08) than those without direct experience/contact with stroke patients (x = 8.00, p = 0.08) seen in Table C1. Specifically, this trend was particularly pronounced among those participants that ranged between 26 - 40 and 41 – 60, which both groups exhibited a significant difference between those contacted in adults (x = 10.73) and middle-aged adults (x = 10.63) and non-contacted participants in 26 - 40 aged (x = 8.12) and 41 - 60 aged (x = 8.85) at the statistical significance level of 95% as shown in Table C4 and Table C5, followed by the age range from 18 to 25, which had an apparent difference at the significance level of 85% between those experienced (x = 8.34) and inexperienced (x = 7.13) as seen in Table C3 . However, this was not the case among the youngest group, as the level of understanding of those who had direct contact with stroke patients (x= 6.59, p = 0.19) was considerably less than that of participants who had not (x = 7.61, p = 0.19) as illustrated in Table C2.

Table C1: t-Test: Contacted and Non-contacted

	Contacted	*Non-contacted*
Mean	9.05454545	7.99550562
Variance	9.10568182	6.57384321
Observations	33	89
Hypothesized Mean Difference	0	
df	50	
t Stat	1.79063324	
P(T<=t) one-tail	0.03970358	

t Critical one-tail	1.67590503
P(T<=t) two-tail	0.07940717
t Critical two-tail	2.00855911

Table C2: t-Test: Contacted and Non-contacted (Adolescents)

	Contacted	*Non-contacted*
Mean	6.5875	7.61363636
Variance	8.25553571	5.68694805
Observations	8	22
Hypothesized Mean Difference	0	
df	11	
t Stat	-0.9033088	
P(T<=t) one-tail	0.19285827	
t Critical one-tail	1.79588482	
P(T<=t) two-tail	0.38571654	
t Critical two-tail	2.20098516	

Table C3: t-Test: Contacted and Non-contacted (Young adults)

	Contacted	*Non-contacted*
Mean	8.34285714	7.125
Variance	7.17285714	5.28456522
Observations	7	24
Hypothesized Mean Difference	0	
df	9	
t Stat	1.09152048	
P(T<=t) one-tail	0.15170055	
t Critical one-tail	1.83311293	
P(T<=t) two-tail	0.3034011	
t Critical two-tail	2.26215716	

Table C4: t-Test: Contacted and Non-contacted (Adults)

	Contacted	*Non-contacted*
Mean	10.7333333	8.11764706
Variance	0.96333333	8.98029412
Observations	3	17
Hypothesized Mean Difference	0	
df	10	
t Stat	2.8381726	
P(T<=t) one-tail	0.00880173	
t Critical one-tail	1.81246112	
P(T<=t) two-tail	0.01760347	

t Critical two-tail	2.22813885

Table C5: t-Test: Contacted and Non-contacted (Middle-aged)

	Contacted	*Non-contacted*
Mean	10.6333333	8.85
Variance	3.5652381	4.9906
Observations	15	26
Hypothesized Mean Difference	0	
df	34	
t Stat	2.72073277	
P(T<=t) one-tail	0.00509575	
t Critical one-tail	1.69092426	
P(T<=t) two-tail	0.0101915	
t Critical two-tail	2.03224451	

3.4 Ages and disease awareness

There was a correlation between the age range of those taking part and their level of awareness regarding the disease, based on statistical analysis. The results demonstrate that participants' awareness of the disease tends to increase with maturity. Young adults (x = 3.39), adults (x = 3.30), and middle-aged adults (x= 3.29) revealed comparable levels of concern. The greatest disparity can be noticed among adolescents (x= 2.7), who were found to have significantly lower levels of concern than the young adults (p=0.01), adults (p=0.06) and middle-aged (p= 0.02). (Seen in Table D1, Table D2, Table D3, Table D4, Table D5, Table D6).

Table D1: t-Test: Adolescents and Young Adults Awareness

	Adolescents	*Young adults*
Mean	2.7	3.38709677
Variance	1.04482759	1.11182796
Observations	30	31
Hypothesized Mean Difference	0	
df	59	
t Stat	-2.5842212	
P(T<=t) one-tail	0.00612736	
t Critical one-tail	1.67109303	
P(T<=t) two-tail	0.01225471	
t Critical two-tail	2.00099538	

Table D2: t-Test: Adolescents and Adults Awareness

	Adolescentss	*Adults*
Mean	2.7	3.3
Variance	1.04482759	1.16842105
Observations	30	20
Hypothesized Mean Difference	0	

df	39
t Stat	-1.9648527
P(T<=t) one-tail	0.02829195
t Critical one-tail	1.68487512
P(T<=t) two-tail	0.05658389
t Critical two-tail	2.02269092

Table D3: t-Test: Adolescents and Middle-aged Awareness

	Adolescents	*Middle-aged*
Mean	2.7	3.29268293
Variance	1.04482759	1.06219512
Observations	30	41
Hypothesized Mean Difference	0	
df	63	
t Stat	-2.4049368	
P(T<=t) one-tail	0.00956266	
t Critical one-tail	1.66940222	
P(T<=t) two-tail	0.01912532	
t Critical two-tail	1.99834054	

Table D4: t-Test: Young Adults and Adults Awareness

	Young adults	*Adults*
Mean	3.38709677	3.3
Variance	1.11182796	1.16842105
Observations	31	20
Hypothesized Mean Difference	0	
df	40	
t Stat	0.28364647	
P(T<=t) one-tail	0.38907217	
t Critical one-tail	1.68385101	
P(T<=t) two-tail	0.77814434	
t Critical two-tail	2.02107539	

Table D5: t-Test: Young Adults and Middle-aged Awareness

	Young adult	*Middle-aged*
Mean	3.38709677	3.29268293
Variance	1.11182796	1.06219512
Observations	31	41
Hypothesized Mean Difference	0	
df	64	
t Stat	0.37987236	
P(T<=t) one-tail	0.35264893	
t Critical one-tail	1.66901303	

P(T<=t) two-tail	0.70529786
t Critical two-tail	1.99772965

Table D6: t-Test: Adults and Middle-aged Awareness

	Adults	*Middle-aged*
Mean	3.3	3.29268293
Variance	1.16842105	1.06219512
Observations	20	41
Hypothesized Mean Difference	0	
df	36	
t Stat	0.02519712	
P(T<=t) one-tail	0.49001845	
t Critical one-tail	1.68829771	
P(T<=t) two-tail	0.98003689	
t Critical two-tail	2.028094	

3.5 Age and exercises

In terms of the correlation of the self-care conducted at each age, it was found to be the highest in adolescents (x= 3.80) followed by young adults (x=3.23) and middle-aged adults (x=3.12) which is moderately lower. Interestingly, the working-age adults ranging from 26 to 40 appeared to have inadequate exercise with levels of 2.75. In addition, based on the t-test analysis, the results revealed the same case for adolescents, who were at the greatest levels compared to young adults (p=0.08), adults (p=0.01) and middle-aged adults (p=0.03). However, the results of the distinction between the adults and the others are shown to be different. It was shown that there wasn't any apparent statistical difference among the young adults (p=0.25) and middle-aged people (0.36) (Seen in Table E1, Table E2, Table E3, Table E4, Table E5, Table E6).

Table E1: t-Test: Adolescents and Young Adults Self-care

	Adolescents	*Young adults*
Mean	3.8	3.22580645
Variance	1.40689655	1.84731183
Observations	30	31
Hypothesized Mean Difference	0	
df	58	
t Stat	1.75958192	
P(T<=t) one-tail	0.04187608	
t Critical one-tail	1.67155276	
P(T<=t) two-tail	0.08375216	
t Critical two-tail	2.00171748	

Table E2: t-Test: Adolescents and Adults Self-care

	Adolescents	*Adults*
Mean	3.8	2.75
Variance	1.40689655	2.19736842

Observations	30	20
Hypothesized Mean Difference	0	
df	35	
t Stat	2.65194665	
P(T<=t) one-tail	0.00597221	
t Critical one-tail	1.68957246	
P(T<=t) two-tail	0.01194441	
t Critical two-tail	2.03010793	

Table E3: t-Test: Adolescents and Middle-aged Self-care

	Adolescents	*Middle-aged*
Mean	3.8	3.12195122
Variance	1.40689655	2.0097561
Observations	30	41
Hypothesized Mean Difference	0	
df	68	
t Stat	2.18936257	
P(T<=t) one-tail	0.01600304	
t Critical one-tail	1.66757228	
P(T<=t) two-tail	0.03200607	
t Critical two-tail	1.99546893	

Table E4: t-Test: Young Adults and Adults Self-care

	Young adults	*Adults*
Mean	3.22580645	2.75
Variance	1.84731183	2.19736842
Observations	31	20
Hypothesized Mean Difference	0	
df	38	
t Stat	1.15584034	
P(T<=t) one-tail	0.12748109	
t Critical one-tail	1.68595446	
P(T<=t) two-tail	0.25496218	
t Critical two-tail	2.02439416	

Table E5: t-Test: Young Adults and Middle-aged Self-care

	Young adults	*Middle-aged*
Mean	3.22580645	3.12195122
Variance	1.84731183	2.0097561
Observations	31	41
Hypothesized Mean Difference	0	
df	66	
t Stat	0.31513394	

P(T<=t) one-tail	0.37682709
t Critical one-tail	1.66827051
P(T<=t) two-tail	0.75365418
t Critical two-tail	1.99656442

Table E6: t-Test: Adults and Middle-aged Self-care

	Adults	*Middle-aged*
Mean	2.75	3.12195122
Variance	2.19736842	2.0097561
Observations	20	41
Hypothesized Mean Difference	0	
df	36	
t Stat	-0.9331297	
P(T<=t) one-tail	0.17848484	
t Critical one-tail	1.68829771	
P(T<=t) two-tail	0.35696968	
t Critical two-tail	2.028094	

4. Discussion

However, they contain a significant difference between their general knowledge and their technical part, which is the section that is found to be struggling by most of the sample. Proponents of the results on general knowledge of the disease, which is comparable to Luan et al. (2021), whose findings also suggest that the sample recognition of stroke symptoms was moderate, which correctly attempted 5.2 out of 12. There are studies that the results of their public awareness levels on the risk factors and warning signs also appeared to contain relatively good understanding, with 59.3% and 68.3%, respectively, being able to correctly answer (Naguib et al.,2020). However, with regards to technical terms, additional education is required so that many people might not fully understand which it can be well supported by the Farraq et al. (2018) studies that aim to investigate public awareness on stroke disease in 4 Egyptian cities by conducting descriptive cross-sectional study. They found that knowledge levels on stroke treatments were inadequate with only approximately 23.9% of participants knowing the appropriate treatments. Similarly, to Sadeghi-Hokmabadi et al. (2019) findings, by focusing on technical aspects, it revealed that only 1.1% of the sample were aware that thrombolytic therapy was a first line of stroke treatments. Furthermore, our study is shown that stroke knowledge is also influenced by gender, with females representing higher levels than that of the males. This phenomenon can be well supported by Sun et al. study (2011) which also found that sex played a related factor of stroke understanding levels as their results suggested that the females acquired higher knowledge levels than the men ($p = 0.001$) also in other studies revealed that female gender is associated with greater awareness of stroke symptoms (Madsen et al., 2015).

Moreover, based on the findings, the experiences and contact with stroke patients can be considered as other factors. The participants who have experienced stroke disease or contacted stroke patients are shown to contain statistical differences and perform better understanding compared to those who had not. Surprisingly, the result is shown to be different from other previous studies from Sullivan et al. (2005) which reveals that there was no significant difference between both of these groups and Ranawaka et al. (2020) whose studies found stroke awareness is not at a satisfactory level in patients with incident stroke and is comparable to patients without stroke.

Therefore, it is recommended in this paper that it be vital for government agencies to help propagate awareness and knowledge regarding fundamental treatments that can assist individuals in avoiding potential risks.

Specifically, a public educational campaign for stroke response should be introduced as the greater number of people who fully understand the method to cope with the disease, the better for them to be safe from the disease. According to Fogle et al. (2003) studies, it was shown that after implementing a 20-week public education campaign, there was a rise in proportion of the participants indicating to respond immediately after experiencing sudden associated symptoms and it suggested that it can improve community awareness on stroke disease. Moreover, FAST guidelines, which shown to be an effective strategy in Wall et al. (2008) studies to improve short term knowledge among the adults aged or elderly to be more recognized on the stroke disease symptoms, can also be introduced within the public educational campaign.

Turning to the correlation of age range, awareness and disease understanding, it was shown that a positive correlation was presented between the age range and their awareness. However, it was not the case with the knowledge levels and participants' age groups. Middle-aged adults appeared to contain relatively good understanding compared to other age-ranges. The outcome was in line with Melnikov et al. (2018) studies which suggested that the highest stroke comprehension was found in the 45 - 64. Notably, some studies revealed that age is negatively correlated with stroke awareness (Nicol et al., 2005; Sun et al., 2011). Thus, stroke knowledge should be known as fundamental knowledge in every age group and early exposure to knowledge related to stroke through the education system is also needed to be prepared. If the curriculum contains these contents, it will impact their lifestyle by avoiding the disease's risk factors and could be well prepared for the immediately unexpected situation.

Lastly, the age group ranged between 12 to 17 which is the youngest sample in the studies, appeared to be the group that contained the highest of exercise levels, but this positive lifestyle did not significantly appear in the other groups. Conducting self-care and performing exercise strategies therefore should be promoted and done by every age group. The rationale behind this is that it is considered as the initial stage in the prevention of cardiovascular and stroke disease. As the greater number of people are looking after themself, the better of health they would receive. Thus, the most effective medication is to look after yourself by preventing the disease and staying healthy.

5. Conclusion

In conclusion, this study underscores the importance of understanding stroke fundamentals to decrease mortality and disability rates. The findings reveal a need for improvement in overall stroke comprehension, particularly in technical aspects, while highlighting that middle-aged adults exhibit the highest understanding. Direct experience or contact with stroke patients correlates with greater disease awareness. To address these gaps, government organizations must prioritize public education efforts, implementing guidelines like FAST and promoting stroke response awareness. By fostering a society that comprehends stroke coping methods, we can reduce the burden of stroke and enhance public health outcomes.

6. Limitation of the study and future recommendation

The group of subjects being studied might not be representative of the entire population, which is a limitation of this study. The study relied on a limited number of participants localized in one location. This restricts the findings' applicability to a wider range of people. To address this limitation, future research should strive to increase the sample size and incorporate participants from a variety of areas in order to gather a more representative sample. Furthermore, altering the contexts and including participants with a variety of conditions related to the research question would increase the validity of the research.

This study's reliance on survey methodology, which may limit the depth of data collected from participants, is another limitation. In some cases, surveys provide limited space for respondents to elaborate on their experiences and perspectives. This may lead to a lack of deep comprehension of the investigated phenomenon. For future

research to overcome this limitation, qualitative methods such as interviews and focus groups should be considered. Interviews would enable researchers to collect detailed descriptions and obtain a deeper understanding of the viewpoints and experiences of participants in relation to the study's topic.

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Challenges and Strategies on Blood Banking and Transfusion Practices During the COVID-19 Pandemic: Ensuring Safe Use of Blood and Blood Products

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Abstract
The COVID-19 pandemic has profoundly impacted healthcare systems worldwide, including blood banking and transfusion practices, resulting in a decrease in the number of blood donors and transfusions. Several challenges faced by blood banks during the pandemic include a reduced donor turnout, shortage of blood products, increased workload, and shortage of staff. These issues have raised concerns regarding the adequacy and safety of the blood supply for patients requiring transfusion. Several strategies including mobile blood donation drives, increasing campaigns, and partnerships among blood banks and healthcare organizations were implemented to address the challenges faced during the pandemic

Keywords: Blood Banking, Problems in Blood Banks, Transfusion During Pandemic, Blood Bank Strategies

1. Introduction

The COVID-19 pandemic has posed significant challenges to healthcare systems worldwide. According to the American Association of Blood Banks (AABB), transfusion practices are among the many areas of healthcare that the pandemic has greatly impacted (AABB, 2020). There have been several reports of a decrease in blood donors and transfusions at the onset of the pandemic, raising concerns about the adequacy and safety of the blood supply for needy patients. In response, the World Health Organization (WHO) has implemented guidelines to ensure the safety of blood donation during the COVID-19 pandemic (WHO, 2020).

In this article, we aim to provide an overview of the challenges faced by blood banking and transfusion practices globally during the COVID-19 pandemic, including the decrease in blood donors, the impact on blood supply, and the risk of transmission of COVID-19 during blood donations. We also discussed the strategies implemented to address these challenges, such as using technology to screen donors and promoting convalescent plasma donation.

2. Review and Discussion

2.1 Donor Eligibility and Screening Protocols

Many countries implemented changes to donor eligibility criteria during the COVID-19 pandemic to ensure the safe use of blood and blood products. These changes aimed to mitigate the risk of transfusion-transmitted infections. Donor eligibility criteria were updated to exclude individuals with recent travel to high-risk areas or those with known exposure to COVID-19 cases (AABB, 2020). Furthermore, individuals who had tested positive for COVID-19 or exhibited symptoms were deferred from donating blood for a specific period, typically 14 to 28 days, to ensure they had fully recovered (AABB, 2020). Temperature checks, mandatory mask-wearing, and social distancing were some of the measures implemented to ensure the safety of donors and staff members during the donation process (AABB, 2020; WHO, 2020).

2.2 Blood Product Safety Measures

Blood banks implemented stringent safety measures to maintain the safety of blood products during the pandemic. Routine tests for infectious diseases, including COVID-19, were conducted to minimize the risk of transfusion-transmitted infections (AABB, 2020). Additionally, blood banks employed pathogen reduction technologies, such as ultraviolet light or chemical treatments, to further enhance the safety of blood products (WHO, 2020). These measures aimed to reduce the potential transmission of the virus through transfusions.

2.3 Challenges Faced by Blood Banks

One of the primary challenges was the decline in blood donations due to reduced donor turnout. Social distancing measures, lockdowns, and fear of exposure to the virus resulted in the cancellation of blood drives and decreased voluntary blood donations. Additionally, disruptions to the supply chain, including transportation restrictions, posed challenges in maintaining an adequate blood supply for healthcare facilities (WHO, 2020).

In Italy, by the first week of March 2020, there was a decrease of about 10% in whole blood donations per week; this numbered 43,000 nationwide compared to their standard donation number of 48,000 (Franchini et al., 2020). They maintained their inventory by temporarily lessening elective surgeries that used high amounts of blood. They also ensured that their reserves of blood kept for strict emergencies were not accessed at all. During the second week of the same month, after vigorous campaigning by their National Blood Center in partnership with their government, they had a 12% increase in whole blood collection, numbering 53,600 from 48,000 worldwide (Franchini et al., 2020).

In India, potential challenges encountered by blood banks include but were not limited to shortage of blood products, safety of blood donor and blood bank staff, and increased workload and shortage of staff (Arcot et al., 2020). In North China, decreased blood donations were a significant challenge owing to lockdown restrictions, and individual and familial apprehensions (Wang et al., 2022). The current challenges faced by blood centers can be related to donor recruitment, reimbursement or funding, the lack of a timely national warehouse capability, and staffing or labor (Association for the Advancement of Blood and Biotherapies, 2022). Other common challenges in blood donor recruitment include fear of contracting COVID-19 at blood donation facilities, inability to conduct donation drives due to lack of resources, and lockdown which has caused closure of public venues and cancellation of gatherings where blood drives are usually conducted (Al-Riyami et al., 2022).

2.4 Strategies Implemented

Blood banks and healthcare organizations implemented several strategies to address the challenges faced during the pandemic. Mobile blood drives and appointment-based donations were organized to encourage voluntary blood donations while ensuring adherence to social distancing guidelines (AABB, 2020). Public awareness campaigns were launched to educate the public on the importance of donating blood and to alleviate concerns about the safety of donating during the pandemic (American Red Cross, 2020). Collaboration between blood banks and healthcare

providers facilitated the collection and appropriate use of convalescent plasma from recovered COVID-19 patients, offering a potential treatment option for severely ill patients (WHO, 2020).

2.5 World Health Organization (WHO) on maintaining an adequate supply of blood and blood products during the COVID-19 Pandemic

The WHO report recommended several measures to prevent COVID-19 transmission during blood donation, including using PPE for blood donation staff and donors, social distancing measures during blood donation, and screening potential donors for COVID-19 symptoms and exposure history (WHO Interim Guidelines, 2020). WHO also recommends using convalescent plasma as a potential treatment option for severe cases of COVID-19 and recommends that blood centers consider collecting and storing convalescent plasma from eligible donors (WHO, 2020). Emphasis was made on promoting voluntary blood donation programs and technology to facilitate contactless blood donation.

The WHO recommendations were useful for blood centers and healthcare organizations worldwide to ensure the continued availability and safety of blood products during the COVID-19 pandemic. However, implementing these recommendations required additional resources and support, particularly in low- and middle-income countries (Pagano et al., 2020).

2.6 Use of Convalescent Plasma

Convalescent plasma, derived from individuals who have recovered from COVID-19 and developed antibodies, has emerged as a potential treatment option. This therapy involves transfusing plasma containing COVID-19-specific antibodies to patients with severe COVID-19 infection (WHO, 2020). Blood banks globally have collaborated with healthcare providers to collect convalescent plasma and ensure its appropriate use for COVID-19 treatment, following established guidelines and protocols.

Several case reports and case series show positive results regarding the utility of convalescent plasma for COVID-19 patient treatment. A study on the different safety metrics after the transfusion of ABO-compatible human COVID-19 convalescent plasma to 5000 hospitalized adults who had a severe or near-life-threatening case of COVID-19 suggested the early safety indicator of COVID-19 convalescent plasma (Joyner et al., 2020). A study by Hartman et al. on 31 patients demonstrated that convalescent plasma reduced ventilatory requirements in patients with both severe and life-threatening diseases (Hartman et al., 2020).

2.7 Promotion of Voluntary Blood Donation

During the COVID-19 pandemic, the promotion of voluntary blood donation was crucial to address the decline in blood donations and ensure an adequate blood supply (WHO, 2020). Blood banks and healthcare organizations implemented various strategies to encourage individuals to donate blood voluntarily while adhering to safety protocols.

One approach was the organization of mobile blood drives and temporary donation centers (WHO, 2020; Miah, 2022; Oreh et al., 2022). These initiatives aimed to bring the donation process closer to potential donors, making it more convenient and accessible. Mobile blood drives can be organized in different locations, such as community centers, schools, and workplaces, allowing individuals to donate blood without traveling to a fixed blood center (WHO, 2020).

Strict hygiene and infection control measures were implemented to ensure the safety of donors and blood bank staff during the pandemic (WHO Interim Guideline, 2020). Donor screening protocols were strengthened to identify potential COVID-19 cases and individuals at higher risk of exposure. Temperature checks, mandatory mask-wearing, hand hygiene, and social distancing measures were implemented at donation sites to minimize the risk of COVID-19 transmission.

Public awareness campaigns were vital in promoting voluntary blood donation during the pandemic (Wang et al., 2022). These campaigns utilized various channels, including social media, television, radio, and print media, to disseminate information about the importance of blood donation, the safety measures in place, and the ongoing need for blood despite the pandemic (Sümnig et al., 2018; WHO, 2020; Wang et al., 2021; Wang et al., 2022). Messages focused on the critical role of blood donors in saving lives and emphasized that donating blood is a safe and essential activity.

In Italy, the Italian National Blood Centre (CNS) continued reinforcing its interest in donating blood products in public hospitals and their different associated collection sites for the smooth and proper collection of blood units involving different donors and healthcare personnel (Franchini et al., 2020). Additionally, partnerships and collaborations between blood banks, healthcare providers, and community organizations were forged to strengthen the promotion of voluntary blood donation (AABB, 2020; WHO, 2020). These collaborations involved engaging with community leaders, conducting educational sessions at schools and colleges, and organizing special donation events targeting specific groups, such as first responders or recovered COVID-19 patients eligible for convalescent plasma donation (WHO, 2020).

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A Literature Review on Regulations Enforced to Reduce Adolescents' Use of E-Cigarette in Thailand

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Abstract
In Thailand, increasing use of e-cigarettes among adolescents poses a significant public health concern. This review demonstrated the multifaceted issues of the problem by exploring the origin of e-cigarettes, factors impacting the broad use of vapes among teenagers, and the guidelines/laws of vaping from government authorities across Asian and Western nations. This study examined the health risks associated with e-cigarette use, dispelled misconceptions regarding public safety, and highlighted the existing treatment programs. Furthermore, the report encompasses frameworks that control teenagers' e-cigarette consumption. Here, we present viewpoints on the situation in Thailand, which are now compared to global experiences. This highlights the urgent need for strict laws to curb the increasing trend in e-cigarette use among adolescents. In this study, the strategy to reduce adolescents' vaping use is proposed with an "ECIG" approach which comprises of Establish e-cigarette prohibition law for adolescents, Control retailers from selling e-cigarette, Individuals' understanding of its negative impact and Guardian's supervision.

Keywords: Cigarette, E-cigarette, Smoking, Adolescents, Vaping, Tobacco

1. Introduction

In the world that is rapidly shaped by technological advancement and drastic change in societal structure, the rising number of electronic cigarettes or e-cigarettes, also called electronic nicotine delivery (ENDS) has become popular among international and Thai adolescents (Evans-Polce *et al.*, 2018; Bhave and Chadi, 2021; Patanavanich *et al.*, 2021; Thepthien *et al.*, 2021; Becker and Rice, 2022). The prevalence of current e-cigarette use in teenagers has remained low since Thai government banned on importation and sales of e-cigarettes (Patanavanich *et al.*, 2021; Thepthien *et al.*, 2021). Aggressive and relentless teenager-targeted marketing from e-cigarette company, readily accessible to vaping products, the cheap price of e-cigarettes, lack of knowledge of harmful health risks, attractive designs and flavors of e-cigarettes are key factors for their popularity among youths (Evans-Polce *et al.*, 2018; Bhave and Chadi, 2021).

2. The Past

2.1. The origin of e-cigarette

Robinson coined the term electronic vaporizer to describe the vaporization of medicinal elements in 1927. This vaporizer was aimed at making it easier to inhale vapor regardless of the burning of the vaporizer. Nonetheless, selling this puffing item was completely banned, except when it was used for medical treatment (Sun *et al.*, 2023). In 1963, Herbert A. Gilbert initiated a patent for fumeless electric cigarettes as a replacement for burning paper and tobacco, based on the heated air facilitated by moisture (Bekki *et al.*, 2014). Despite Gilbert's ground-breaking invention, his cigarette did not receive attention from all manufacturers, who should have developed its product lines. Nonetheless, it was not until 2003 that Hon Lik, a pharmacologist in China, improved the availability of e-cigarettes (Bekki *et al.*, 2014). In fact, he was inspired to have a new idea for helping his father, who was susceptible to lung cancer and cigarette addiction, completely cease smoking habits (Bekki *et al.*, 2014; Nayir *et al.*, 2016).

3. Factors contributing to the use of e-cigarette among adolescents

Puffing e-cigarettes by teen smokers is significantly attributed to various sources, embracing social pressure from friends as well as marketing and advertising gimmicks, together with personal predilection. Disclosing and promoting e-cigarette marketing and advertising are associated with facilitating the consumption of this puffing item by prospective users with high curiosity. Moreover, advertising and marketing ENDS through social media have been found to be significantly associated with strengthening friendly relationships. Indeed, the chances of puffing e-cigarettes used by friends are twice as high as those seen via social media and advertisements when compared to other sources of media (Groom *et al.*, 2021). According to the initial findings, quite a few teenagers were most likely to not use vaporizing cigarettes to cut off their smoking habits.

On the contrary, the use of e-cigarettes significantly derives from mental acquisitiveness, attractiveness of diverse tastes, and social influence by people around. Moreover, the pleasure from smoking contributes to e-cigarette use. On this basis, the causes of puffing e-cigarettes among minors differ greatly, contributing to separate research, as proposed by veteran academics (Patrick *et al.*, 2016). A group of student samples who reported their puffing experience were asked about the main reasons for their inhaling with the query: What are the main causes of your use of vaping items, such as e-cigarettes? As for their responses, 10 main reasons were revealed: "to test and experience what it actually is", "to please its good flavors", "to ease their boredom", "to enjoy life with their friends", "to relax or reduce stress", "to prove its appeal", "to cease smoking traditional cigarettes", "to substitute normal banned cigarettes", "to get it intoxicated", and "to soothe their smoking addiction" (Evans-Polce *et al.*, 2018).

4. Policy development about vaping in Asian and Western countries

The government's opting for policies responsible for regulating tobacco could have an impact on the e-cigarette vaping habits of students as well as their contribution to controlling tobacco. The nations in the Asia-Pacific region are being exposed to the tobacco landscape with great revolution and improvement, while the rules and regulations responsible for easing the adverse impacts of tobacco on public health are being formulated and made much more efficient than ever before. It was not until 2013 that the crucial report made by the WHO Tobacco Free Initiative aimed to assist many nations worldwide in fortifying policies for precluding e-cigarette smoking in public areas where these items are totally banned and disallowed for sales to buyers with no legal rights for purchasing at certain places in which e-cigarettes are entirely discouraged for use. Meanwhile, there are strict limitations against marketing and advertising e-cigarettes in common with regular cigarette counterparts, whereas the practice of e-cigarette tastes is utterly prohibited, and tobacco companies are precluded from making advertisements to help users quit smoking by turning to e-cigarette use, except when approved by suitable regulatory agencies. Subsequently, as of 2017, the Association of Pacific Rim Universities (APRU) Global Health Program officially

acknowledged the rising rates of e-cigarette use among student smokers. This act aimed to make public health professionals and policymakers more conscious of the adverse effects of e-cigarettes as a critical issue for adolescent smokers in certain regions. Moreover, they are intended to provide in-depth information that acts as an intervention for addressing this problem (Wipfli *et al.*, 2020).

In many European countries, minors with relatively low socioeconomic status are more likely to smoke e-cigarettes than those with higher socioeconomic status. On this basis, the enforcement of school policies by precluding students with diverse socioeconomic contexts from smoking e-cigarettes in school can be highly effective since they are inevitably subject to school settings. Additionally, smoking policies in many schools differ in line with their enforcement and implementation. However, the smoking habits and behaviors of students may be significantly related to their perception of the smoking policies of each academic institution in which they are studying. According to many studies, the chance of cigarette smoking among students is prone to decrease if they clearly know the anti-smoking rules and regulations strictly enforced by that school (Kuipers *et al.*, 2016). It was also revealed that e-cigarettes have been incrementally well-received among young and mature smokers in the EU, Canada, and the United States since e-cigarettes were granted international patents, thus making them legally available for sale in global markets in 2007 (Becker and Rice, 2022). Likewise, not only the EU, but also the United States and Canada comply with the approaches of the federal government responsible for regulating e-cigarettes. In this way, the EU, the US, and Canadian federal governments collaboratively determine policy frameworks, thus requiring all states and provinces to have autonomy in implementing extra rules and regulations against the use of e-cigarettes. In the meantime, not only the member states but also the European Parliament in the EU collaboratively take responsibility for selling, manufacturing, producing, distributing, and even promoting cigarette items that are strictly controlled both domestically and internationally. Nevertheless, all rules and regulations enforcing the use of e-cigarettes must be based on the guidelines and approaches required by the World Health Organization Framework Convention on Tobacco Control (FCTC). In addition, as of 2014, the European Parliament approved the EU so that it could take the Tobacco Products Directive (TPD) into effect. Consequently, it was not until May 2016 that the Tobacco Products Directive became effective in the EU member states. Canada became a member of the FCTC, which enabled the implementation of the Tobacco and Vaping Products Act (TVPA) as of May 2018. Consequently, all provinces, territories, and municipalities in Canada legitimately received regulatory frameworks, allowing them to take extra restrictions, impositions, and regulations on e-cigarettes before 2018 (Snell *et al.*, 2021).

5. The present

5.1. Health risks

Although e-cigarette particles are less dangerous than the components breathed during smoking, they adversely affect the physical health of users, especially the respiratory system. Heavy metals from batteries and coils heated by e-cigarette devices are responsible for making smokers vulnerable to toxins or carcinogens, which substantially harm their hearts and lungs, although the long-term effects of e-cigarette exposure are unpredictable. Respiratory irritants can also be ascribed to E-liquid bases such as propylene glycol (Becker and Rice, 2022).

The national epidemic of e-cigarettes or vaping product use-associated lung injury (EVALI) marked the first instance of a vaping-linked illness affecting a considerable number of individuals. Essentially, EVALI represents chemical injury from inhaled substances, likely resulting from the heating, aerosolization, and inhalation of Vitamin E found in THC liquids and vapor devices. Analysis of the respiratory passages and lungs revealed a pattern of epithelial and alveolar damage (Casey *et al.*, 2020). Radiographic detection in smoking teens exposed to EVALI includes centrilobular ground-glass nodules and opacities, with subpleural sparing. There is also an explanation for puffing-associated health risks. Exposure to e-cigarette liquids is also associated with seizures. Meanwhile, e-cigarettes negatively affect oral health, although they are less severe than normal cigarettes are. Similar to normal cigarettes, not only can smoking fumes of used e-cigarettes cause health risks, but it also contaminates indoor air quality, despite this secondhand e-cigarette causing less severity than its cigarette counterpart. It is highly possible that teenagers violated social distancing while COVID-19 was spreading (Becker

and Rice, 2022), thus exposing them to the virus, which is mediated via a neurobiologically determined valuation of risks, while smokers who share e-cigarette devices with other users without wearing masks made them increasingly exposed to the risks of spreading and illness suffered by family members when they return home.

6. Misconceptions about using e-cigarette

A range of misconceptions regarding e-cigarettes have been identified in the literature. First, it is commonly misunderstood that e-cigarettes are less harmful than traditional cigarettes are. For example, non-white respondents believed that puffing e-cigarettes was less dangerous than smoking normal cigarettes. This misconception is possibly attributed to the ability of e-cigarettes to avoid dangerous compounds, such as arsenic, which are normally abundant in normal cigarettes. In addition, this misperception may be derived from the variety of tastes and beautiful designs of e-cigarettes, making many smokers believe that they are relatively safe (Golan *et al.*, 2023). In addition, many vapers believe that positive moods can be enhanced by vaping. However, research has revealed that an array of mental health symptoms, especially anxiety, depression, and even thinking about suicide, are significantly related to e-cigarette smoking (Javed *et al.*, 2022).

7. Programs of treatment

Since evidence-based pharmaceutical treatments applied to teenagers addicted to e-cigarette puffing cannot be officially confirmed, behavioral strategies have become the first step in treating patients addicted to e-cigarette smoking. These strategies are considered efficient in ceasing e-cigarette addiction, and include individual and group consultations, interviews for building motivation, cognitive and behavioral therapy, emergency management, conscious intervention, and strategies based on websites and smartphones. In addition to behavioral strategies, patches, gums, and lozenges can be used as efficient substitutes for nicotine to treat teenagers with e-cigarette addiction when e-cigarettes contain high levels of nicotine. Anti-craving drugs such as bupropion and varenicline can also be used as efficient substitutes for nicotine. It was not until January 2020 that the new policy statement was released by the Society for Adolescence and Medicine in collaboration with a group of Adolescent Medicine Providers from India, Canada, and the United States, including the United Kingdom, who were responsible for recommending and guiding teenagers to learn how to protect themselves from the dangers of e-cigarette smoking, while being advocated by policies for regulating the sales of e-cigarette products to adolescent consumers. In the meantime, support for public health–based education campaigns and educational curricula adopted by school students, community programs, and health providers reminding the dangerous effects of e-cigarettes on health are applied to teens and early adults (AYAs). At the same time, the researchers responsible for developing the guidelines based on evidence to preclude the dangers of e-cigarette smoking, as well as to quit vaping behaviors, also contributed to AYAs. Concurrently, however, these health providers need to receive more training to screen for e-cigarette smoking integrated into regular health visits for AYAs, together with increasing consultation based on evidence, as well as resources responsible for ceasing e-cigarette smoking habits (Bhave and Chadi, 2021).

8. Laws that control the use of e-cigarette by teens

The laws that affect e-cigarette consumption play an important role in controlling and restricting the sales, taxation, and marketing of e-cigarettes, as well as access to teen consumers when e-cigarettes are considered to be different from traditional cigarettes. Unless extra rules for the use of e-cigarettes are applied in places where smoking is prohibited, people are encouraged to continue their e-cigarette smoking habits, rather than complete cessation. Additionally, unless similar smoke-free regulations are applied to e-cigarettes, imitation of e-cigarette smoking can be multiplied, which is antagonistic to efforts to reduce the use of e-cigarettes and interfere with attempts to control their use.

It is very difficult to identify what e-cigarettes are defined because of their different names, such as e-cigarettes, e-hookahs, vape-pens, hookah pens, and personal vaporizers, together with various types and brands of e-cigarettes

existing, while consumers can build e-cigarette devices modified by themselves. It was not until 2010 that e-cigarettes were disapproved in court to be accepted as medical devices if they were not marketed for medical objectives. Moreover, e-cigarettes could not be regulated as tobacco derivatives if the FDA was negligent to keep them protected by the Tobacco Control Act. Subsequently, in April 2014, the FDA proposed a rule for regulating e-cigarettes that is not different from tobacco items. However, in October 2014, this attempt remained outstanding, making e-cigarettes unfederally defined. Nonetheless, the sale and use of e-cigarettes have been regulated by the laws of states and local governments. Although e-cigarette standards are being controlled by the FDA, they are still controlled by the laws prescribed by the states and localities, as they are enabled by the Tobacco Control Act to legitimately obtain the use, sales, distribution, access, and marketing of e-cigarette products, unless they are not considered as such (Lempert *et al.*, 2016).

9. The Prospect

9.1. What is going on and what will be continuing in Thailand?

Since 2015, the sale and import of e-cigarettes has been prohibited in Thailand for eight consecutive years, with the aim of preventing teens from vaping addiction (Patanavanich *et al.*, 2021; Thepthien *et al.*, 2021). The continuous low ubiquity of e-cigarette uses by teenagers, as presented in this study, was possibly attributed to the outcomes of banning e-cigarettes, as the prevalence of e-cigarettes did not show a statistically significant difference from the use of e-cigarettes. One explanation for the frequent use of e-cigarettes in Thailand compared to other nations where e-cigarettes are prohibited was possibly put down to no conformity with the prohibition on tobacco, advertising, promotion, and sponsorship (TAPS) in Thailand, particularly through social networking sites as the most popular distribution channel, allowing the tobacco industry to access these target consumers (Patanavanich *et al.*, 2021). Another serious concern is the lack of knowledge about the adverse effects of e-cigarette use.

There is an apparent limitation to school-based anti-smoking education programs and schools devoid of smoking, with emphasis on information. However, based on existing literature, two main priorities have been emphasized in Thailand. The first priority is to prohibit minors entirely from initially smoking e-cigarettes and being addicted to vaping, whereas the second is to take stronger laws into effect and penalize perpetrators who violate the rules, particularly with regard to marketing e-cigarette products online (Patanavanich *et al.*, 2021). In parallel, schools should increasingly adopt effective anti-smoking programs to address e-cigarette problems, as well as to provide parents and the public with knowledge about the harmful effects of e-cigarette products as well as the risks suffered by non-smokers who are vulnerable to secondhand smoke from e-cigarette products (Thepthien *et al.*, 2021).

10. Regulatory Approaches for Curbing Adolescent E-Cigarette Usage in Thailand

In this paper, we propose an acronym for defining an approach to reducing adolescents' vaping behaviors. The acronym is ECIG, which stands for Establish an e-cigarette prohibition law for adolescents, Control retailers from selling e-cigarettes to people across all ages, Individuals' understanding of the negative effects of e-cigarettes, and Guardian's supervision.

E: Establish e-cigarette prohibition law for adolescents

Despite existing regulations, it is important to address the use of e-cigarettes by teenagers. It is crucial to ensure that teenagers abstain from smoking e-cigarettes irrespective of their justification. Nonetheless, e-cigarette devices are popular among teenagers despite regulations being enforced. The sources of these breaches should be identified and addressed. One of the most effective strategies is to take laws into effect and penalize those who cannot abstain from e-cigarette smoking. Moreover, should minors be educated about compliance with the laws and the outcomes of non-conformity to the laws?

C: Control retailers from selling e-cigarette to people across all ages

Although many countries have enforced legislation to curb e-cigarette puffing, retailers continue to distribute e-cigarette products sneakily, leading to conspiracy practices and illegal enterprises. Meanwhile, e-cigarette products are prevalent on online sites and e-commerce markets without conformity to legal status. Accordingly, it is necessary to adopt a resolute stance to protect teens, adults, and nonsmokers from exposure to potential damage to the lungs and secondhand smoke by reinforcing measures to curb these smoking activities.

I: Individuals' understanding of the negative effects of e-cigarette

In a world greatly influenced by social media, audiences find it easy to access abundant information on various topics, and this information can be absorbed by people very quickly, regardless of whether it is accurate. Consequently, the Internet has become overwhelmingly circulated with plentiful fake news, exposing most people to deception. Additionally, fake news is responsible for causing damage by getting audiences to form misconceptions regarding the advantages and disadvantages of e-cigarettes. Accordingly, fake news and false information must be eradicated because negligence in this act can lead naive teenagers to misunderstand and continue using e-cigarette products in a negative manner.

G: Guardian's supervision

To promote the safety of these teenagers, it is important that parents and guardians opt for parenting approaches that are engaged in having the acts of children closely supervised and overseen. Meanwhile, they must take responsibility for acknowledging the likelihood of e-cigarette use by their children, which poses significant damage to their physical condition. In parallel, these children must be educated about e-cigarette smoking and its potential adverse effects on their health.

11. Conclusion

This study revealed the intricate challenges posed by the increasing use of e-cigarettes among Thai teenagers. The origins of e-cigarettes, the factors driving their popularity among users, and global regulations have been explored. The health risks associated with e-cigarettes are illuminated to dispel misconceptions and support informed decision making. To reverse this trend, urgent action must be implemented through stringent regulations and comprehensive education. Currently, Thailand is facing a crucial moment. Through collaborative efforts and public awareness, we can pave the way for positive societal change.

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Ultrasound Shear Wave Elastography in the Evaluation of Liver Fibrosis

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Abstract
Background: Chronic hepatitis B virus (HBV) infection affects about 296 million people worldwide and is the leading etiology of cirrhosis and liver cancer globally. In China, chronic hepatitis B has grown to be a significant public health issue. NAFLD (non-alcoholic fatty liver disease) is one of the primary causes of cirrhosis in the globe. Up to 10.3% of NAFLD patients, according to the National Health and Nutrition Examination Survey, had advanced fibrosis. These findings suggest that the real-time Shear wave elastography (SWE) can be used for the assessment of significant fibrosis, sever fibrosis and Cirrhosis. Objective: To determine the ultrasound shear wave elastography in the evaluation of liver fibrosis. Methods: A cross-sectional study was conducted at First affiliated hospital of Xinjiang Medical university, which was performed between January 2020 and March 2023. The total patients in our study was 118. In 118 consecutive patients who underwent Ultrasound Shear wave elastography (SWE) before their scheduled liver biopsy (59 men, 59 women). We used Michael Mindray ultrasound machine and its frequency was C6-1. The stages of liver fibrosis according to the METAVIR classification system. Results: F2 stage of fibrosis is more as compare as compare to others. Liver fibrosis is more common in females as comapre to males. According to the age males have higher risk as compare to females. Total patients in our study was 118. Mean age for males patienst were 44.8983 and for females 48.9492. MEAN±SD of Alanine aminotransferase (ALT) was 92.6±116.14 u/L. The frequency of patients with F0 was 33 (28.0 %), F1 was 5 (4.2%), F2 was 58 (49.2%), F3 was 9 (7.6%) F4 was 13 (11.0%). Frequency of no fatty liver was 49, mild fatty liver was 39, moderate fatty liver was 8, sever fatty liver was 22. Hepatitis B was present in 96 patients and was not present in 22 patients out of 118. Hepatitis C was present in 116 patients and was not present in 2 patients out of 118 (1.7). P-value of hepatitis B is 0.34. P-value of hepatitis C is 1.0. P-value of stages of Liver fibrosis with respect to gender is 0.005. Conclusion: Our result concluded that fibrosis stage F2 patients are more in our study (Heaptitis B). Liver fibrosis is more common in females as comapre to males. According to the age males have higher risk as compare to females. Shear wave elastography (SWE) is a straightforward, quick, and repeatable technique for noninvasively assessing liver fibrosis. Benefits include its low cost and global availability.

Keywords: Ultrasound Shear Wave Elastography (SWE), Liver Fibrosis, Chronic Hepatitis B Virus (HBV) and Hepatitis C

1. Introduction

Chronic hepatitis B virus (HBV) infection affects about 296 million people worldwide and is the principal etiology of cirrhosis and liver cancer globally (Hsu et al., 2023). In China, chronic hepatitis B has emerged as a major public health issue (Zheng et al., 2020). Liver biopsy is now the gold standard for determining if someone has cirrhosis or liver fibrosis (Karkmann et al., 2018). Between 20 and 30 percent of persons in Western countries have nonalcoholic fatty liver disease (NAFLD) (Vernon et al., 2011). The reference standard for grading steatosis and inflammation, two characteristics unique to steatohepatitis, and staging fibrosis, a measure of the severity of liver disease, is often liver biopsy (Kleiner et al., 2005; Sanyal et al., 2005). However, liver biopsy is an intrusive procedure that comes with risk of bleeding, discomfort, and inaccurate sample (Fernandez et al., 2011; Myers et al., 2008). As a result, a noninvasive method is required for the evaluation of hepatic steatohepatitis. Cirrhosis, cancer, and liver failure can develop from hepatic fibrosis. Depending on the degree of liver fibrosis, many clinical therapy modalities exist (Barr et al., 2020). The creation of elasticity-based ultrasonography (US) methods, which assess the speed of elastic shear waves to offer a quantitative assessment of liver stiffness represents a significant advancement in the noninvasive examination of liver fibrosis (Bamber et al., 2013; Grgurevic et al., 2015). In particular for cirrhosis, it has demonstrated high accuracy in fibrosis detection (Friedrich et al., 2008; Bohte et al., 2014). Elastography can only measure stiffness, despite the fact that liver stiffness is often closely linked with the degree of fibrosis (Goodman 2007). Cirrhotic nodules are one example of a fibrotic formation that can grow to be bigger than the US wavelength (Toyoda et al., 2009). One of the main causes of cirrhosis globally is non-alcoholic fatty liver disease (NAFLD) (Gbd, 2017). NAFLD is one of the leading and fastest-growing causes of chronic liver disease worldwide followed by obesity and insulin resistance (Younossi et al., 2016; Younossi et al., 2018). Up to 10.3% of NAFLD patients had advanced fibrosis, according to the National Health and Nutrition Examination Survey (Le et al., 2017). These results imply that real-time SWE can be utilized to evaluate cirrhosis, severe fibrosis, and substantial fibrosis (Jing et al., 2017).

2. Materials and Methods

A cross-sectional study was conducted at First affiliated hospital of Xinjiang Medical University, which was performed between January 2020 and March 2023, The total patients in our study was 118. In 118 consecutive patients who underwent Ultrasound Shear wave elastography (SWE) before their scheduled liver biopsy (59 men, 59 women). We used Michael Mindray ultrasound machine and its frequency was C6-1. The stages of liver fibrosis according to the METAVIR classification system. Informed consent was obtained from all patients. Shear wave elastography (SWE) measurements were obtained at four sites in the liver. Biopsy specimens were reviewed in a blinded manner by a pathologist using METAVIR criteria. SWE measurements and biopsy results were compared by using the Spearman correlation and receiver operating characteristic (ROC) curve analysis. Data was tabulated and analyzed by SPSS.

2.1. Clinical and laboratory examination

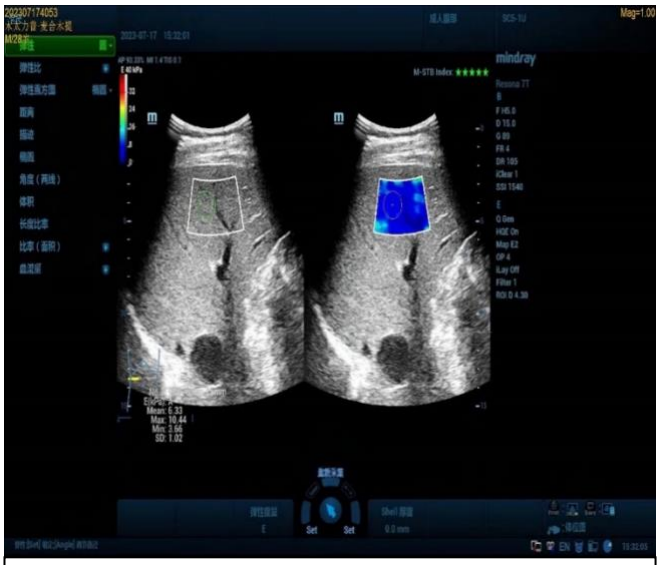
Weight, sex, and age were noted. After the patients had fasted for eight hours, venous blood samples were taken in order to evaluate the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl-transpeptidase (GGT), and alkaline phosphatase (ALP). Body mass index (BMI).

3. Results

According to our study total patients were 118, Distribution of patients according to gender was (59 were males and 59 were females). Distribution of patients according to mean age (out of 118 patients, 44.8983 were males and 48.9492 were females). Distribution of patients according to mean age of standard deviation (16.16 were males and 12.92 were females). Graphical Representation of gender represent that both gender are same in number 59 were males and 59 were females.

Table 1: Distribution of patients according to gender and mean age *(n=118)*

Variable	Frequency	Percentage
Gender:		
Male	59	100.0
Female	59	100.0
Total	118	100%
	Mean	**SD**
Age		
Male	44.8983	16.16
Female	48.9492	12.92
Total Age	46.92	14.71



F0: No scarring (No Fibrosis)

Mean and Standard Deviation (SD) of liver Function

MEAN±SD of Alanine aminotransferase (ALT) was 92.6±116.14 u/L, MEAN±SD of Aspartate aminotransferase (AST) was 74.23±81.75 u/L, MEAN±SD of Alkaline phosphate (ALP) was 302.46±999.9 u/L, MEAN±SD of Total Bilirubin (TBIL) was 55.03±204.98 umol/L, MEAN±SD of bilirubin test (DBIL) was 7.28±21.3 umol/L, MEAN±SD of Gamma-glutamyl transferase (GGT) was 172.80±711.1 u/L, MEAN±SD of Creatine kinase (CNE) was 4938.51±2287.2 u/L, MEAN±SD of Blood nitrogen urea (BUN) was 43.59±31.5 mmol/L,

Table 2: Mean and SD of enrolled patients (*n=118)*

Variables	MEAN±SD
ALT	92.6±116.14
AST	74.23±81.75
ALP	302.46±999.9
TBIL	55.03±204.98
DBIL	7.28±21.3
GGT	172.80±711.1
CNE	4938.51±2287.2
BUN	43.59±31.5

F1: Minimal Scarring

The stages of Liver fibrosis according to the METAVIR classification system *(n=118),*
The frequency of patients with F0 was 33 (28.0 %), The frequency of patients with F1 was 5 (4.2%)
The frequency of patients with F2 was 58 (49.2%), The frequency of patients with F3 was 9 (7.6%)
The frequency of patients with F4 was 13 (11.0%)

In the above pie graph F2: 49%, F0: 28%, F4: 11%, F3: 8% and F1: 4 %.

Distribution of patients on the basis of Fatty Liver (n=118). Frequency of no fatty liver was 49 and its percentage was 41.5 %. Frequency of mild fatty liver was 39 and its percentage was 33.1 %. Frequency of moderate fatty liver was 8 and its percentage was 6.8 %. Frequency of sever fatty liver was 22 and its percentage was 18.6 %.

Table 3: Distribution of patients on the basis of Fatty Liver (*n=118)*

Fatty liver	Frequency	Percentage
No	49	41.5
Mild	39	33.1
Moderate	8	6.8
Severe	22	18.6
Total	118	100.0

F2: Scarring has occurred and extended outside the liver area (Significant Fibrosis)

Table 3: The mean BMI of enrolled patients *(n=118)*

BMI
24.10±4.28

Distribution of patients on the basis of hepatitis B and hepatitis C (n=118)

Hepatitis B was present in 96 patients out of 118 (81.4%), Hepatitis B was not present in 22 patients out of 118 (18.6). Hepatitis C was present in 116 patients out of 118 (98.3%), Hepatitis C was not present in 2 patients out of 118 (1.7).

Distribution of patients on the basis of Hepatitis B and Hepatitis C with respect to gender (n=118). Hepatitis B was present in male patients 58 (98.3%) and Hepatitis B was not present in male patients 1 (1.7%). Hepatitis B was present in female patients 58 (98.3%) and Hepatitis B was not present in female patients 1 (1.7%).
P-value of hepatitis B is 0.34.

Hepatitis C was present in male patients 46 (78.0%) and Hepatitis C was not present in male patients 13 (22.0%). Hepatitis C was present in female patients 50 (84.7%) and Hepatitis C was not present in female patients 9 (15.3 %).
P-value of hepatitis C is 1.0

Table 4: Distribution of patients on the basis of Hep B and Hep C with respect to gender (*n=118)*

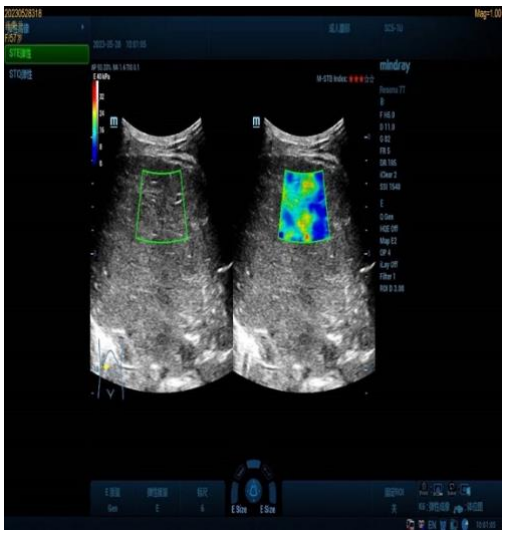
		Hepatitis B	
Gender	Frequency	Percentage	P-Value
MALE			
YES	58	98.3	0.34 Not significant
N0	1	1.7	
FEMALE			
YES	58	98.3	
NO	1	1.7	
	Hepatitis C		
Male			
YES	46	78.0	1.0 Not significant
NO	13	22.0	
Female			
YES	50	84.7	
NO	9	15.3	

F3: Fibrosis spreading and forming bridges with other fibrotic liver areas (Sever Fibrosis)

Distribution of patients on the basis of Stages of Liver fibrosis with respect to gender (*n=118).*Frequency of F0 in male Patients was 25 (42.4%), Frequency of F1 in male Patients was 1 (1.7%), Frequency of F2 in male Patients was 26 (44.1%), Frequency of F3 in male Patients was 2 (3.4%), Frequency of F4 in male Patients was 5 (8.5%). Frequency of F0 in female Patients was 8 (13.6%), Frequency of F1 in female Patients was 4 (6.8%), Frequency of F2 in female Patients was 32 (54.2%), Frequency of F3 in female Patients was 7 (11.9%), Frequency of F4 in female Patients was 8 (13.6%).

Table 5: Distribution of patients on the basis of Stages of fibrosis with respect to gender (*n=118)*

		Stages of fibrosis	
Gender	Frequency	Percentage	P-Value
MALE			
F0	25	42.4	0.005 significant
F1	1	1.7	
F2	26	44.1	
F3	2	3.4	
F4	5	8.5	
FEMALE			
F0	8	13.6	
F1	4	6.8	
F2	32	54.2	
F3	7	11.9	
F4	8	13.6	



F4: Cirrhosis or advanced scarring

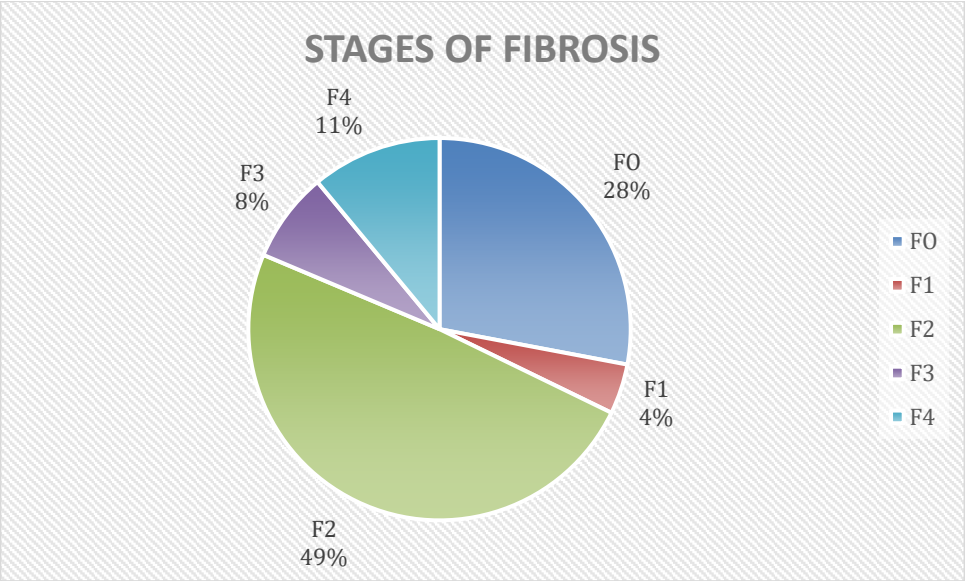


Figure 6: Pie Graph Representation of Stages of Fibrosis

P-value of stages of Liver fibrosis with respect to gender is 0.005.

4. Discussion

In this study, the diagnostic precision of real-time Shear wave elastography (SWE) in estimating liver fibrosis was compared against histology. These findings suggest that real-time SWE can be used for the assessment of significant fibrosis, severe fibrosis, and cirrhosis (Jing et al., 2017). Currently, the pathological evaluation of hepatic wound tissue is still required for the diagnosis of liver fibrosis. The approach is intrusive, hence its widespread usage in clinical practice is currently restricted. The development of a non-invasive diagnostic indicator for liver fibrosis has received a lot of attention (Lu et al., 2003). In this prospective cross-sectional study, we evaluated the ideal region from which to obtain measurements and estimated the diagnostic accuracy of SWE for liver fibrosis estimation in patients with chronic liver disease CLD and hepatitis C virus HCV using liver biopsy as the standard of reference (Samir et al., 2015). In clinical practice, the precise and non-invasive categorization of liver fibrosis is of utmost importance. Recently, a deep learning system for employing ultrasound shear wave elastography to stage liver fibrosis was published, and it performed well (Yasaka et al., 2018). Histopathologically, hepatic fibrosis is a consequence of the excessive accumulation of extracellular matrix components in the liver. This process is caused by a wound healing response to persistent liver damage, inducing hepatic stellate cell activation, high alpha smooth muscle actin production, and collagen type I and III secretion, and can progress to cirrhosis (Crespo et al., 2016). Liver fibrosis results from excessive extracellular matrix accumulation due to injury and main to cirrhosis, cancer and death (Ullah et al., 2022). Imaging allows for the assembling of sufficient detailed information on the overall levels of probe accumulation in the tissue or organ of interest due to the much clearer images of the anatomical and spatial distribution of the probe (Tuguntaev et al., 2022).

5. Conclusion

Our result concluded that F2 fibrotic patients are more in our study (Heaptitis B). Liver fibrosis is more common in females as comapre to males. According to the age males have higher risk as compare to females. Shear wave elastography (SWE) is a straight forward, quick, and repeatable technique for noninvasively assessing liver fibrosis. Benefits include its low cost and global availability.

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Standardization of the Medication Review Process in Primary Care: A Quality Improvement Project

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Abstract
Introduction: Medication review process (MRP), especially pertaining to prescription refills, poses significant challenges in primary care. If MRPs are not conducted with care, then patients come under the risk of drug-related problems (DRPs), including receiving incorrect medication or dosage, therapeutic duplications, refilling a previously discontinued medication, nonadherence, and overdosing. Aim and Research Gap: Standardized approaches to medication review are currently limited in practice. Also, reviewing and reconciling patient medications is time-consuming and contributes to practitioner burnout. Therefore, this quality improvement project aimed to incorporate simple medication review protocols into patient care, a standardized rooming experience, and updated medication refill procedures to lessen the burden of refill requests on a primary healthcare facility, and to improve patient and healthcare staff safety and satisfaction in the USA. Methods: An evidence-based method, lean process improvement approach was used. An interdisciplinary team was created to map out the medication refill process. Convenience sampling was used to collect data, including phone calls, from November 1, 2021, to November 2, 2022, from the practice's Nextgen EHR system. The names of highly prescribed medications and the frequency of these medications as being re-prescribed were quantified and the interdisciplinary team met to discuss opportunities for improvement. Results: This quality improvement project analyzed the challenges in a single United States primary care facility's medication refill process and suggested simple improvements. The facility received significantly fewer refill phone calls after streamlining communication to patients to bring their medication prescription bottles to appointments, standardizing rooming experiences, updating clinic protocols and workflows, and training staff to complete medication verification ($p < 0.001$). Discussion and Conclusion: The findings from this quality improvement project support the necessity of standardized protocols in a medication review and refill processes in primary care settings with its positive impact impacts.

Keywords: Medication Review, Re-prescribing, Electronic Health Records, Medication Protocol, Drug Related Problem, Polypharmacy, Medication Reconciliation, Attrition

1. Introduction

The medication review process (MRP) is a systematic and structured critical evaluation of a patient's medications to reach a treatment agreement, optimize medication use, minimize drug-related problems (DRPs), improve health outcomes, and reduce waste (Alghadeer et al., 2021; Assab et al., 2022). As such, MRP is one of the most critical

components of primary care. The goals of proper medication management include the reduction of errors in the process, increased safety, better outcomes, decreased provider workload, reduced burnout, and increased satisfaction for both medical teams and patients.

Primary care prescription processes, especially for re-prescribed medications, can place patients at significant risk if not undertaken with care. This can be due to the communication gap between follow-up appointments and laboratory tests. Some prescribers prefer electronic prescription refill requests, while others favor telephone requests through an office call center or front desk staff. When available, some prescribers may defer such requests to be handled by pharmacists as supported by collaborative practice agreements or clinical protocols. While professional organizations have published various guidelines in this area, there are no universal, standardized approaches in prescription processes leading to unintended effects.

Today, roughly 75% of primary care prescribing is for re-prescribed medications typically used for chronic illnesses (Alghadeer et al., 2021). One study found that about 57% of patients with re-prescribed medication have at least one drug-related problem (DRP) or medication change, including receiving the wrong medication or dosage, therapeutic duplications, refilling a previously discontinued medication, nonadherence, and overdosing (Alghadeer et al., 2021). Furthermore, one long-term surveillance study in the United States concluded a 2.8% mortality rate associated with the adverse effects of inefficient medication review processes (Alghadeer et al., 2021).

Importantly, specific populations are more prone to greater medication errors, such as the elderly and those transitioning care from an intensive care setting to a home or from one healthcare setting to another. For example, 46% to 74% of intensive care patients experience medication errors (Bourne et al., 2022). Medication-related admissions to the hospital are frequent in older adults as well (Dautzenberg et al., 2021). More than 40% of people in the United States who are older than 65 take five or more prescription medications regularly for chronic disease control or prevention (Bloomfield et al., 2020). Polypharmacy is associated with an increased risk of falls, hospitalizations, cognitive impairments, and mortality in the older adult population, making the number of medications, a person is on, one of the most important predictors of adverse effects (Bloomfield et al., 2020).

Moreover, effective medication review heavily draws upon a facility's staff and resources. These time and resource burdens are problematic in prescription refill processes. Overburden and exhaustion in healthcare practitioners is well established in the literature, including nurses and physicians, which is not only associated with attrition but also compromises the well-being of practitioners and patients alike (Dunham, 2022).

Furthermore, medication reconciliation involves obtaining a list of all medications the patient is taking. This can be performed by various healthcare team members depending on state regulations, authority guidelines, and institutional policies. Pre-visit planning is essential to medication reconciliation, whereas several opportunities become available to confirm prescriptions. There can be opportunities to ensure patient medications by various means, such as when patients make appointments, when appointments are confirmed by medical staff, before a visit via patient portals, and while waiting for the practitioner in the room. In addition, patients can bring their medications to the appointment, eliminating discrepancies in medication misspellings, dosages, and frequencies. Refill dates and other prescribing information are also readily available on the bottles.

Medication reconciliation and review are time-consuming, leading to overprescribing and perpetuation of DRPs. Furthermore, insurers have responded to the increase in prescription volumes by placing hurdles in the process, such as prior authorizations (Dunham, 2022). More than 80% of all primary care visits involve medications, and, on average, physicians refill about ten prescriptions per day for individuals who do not have in-person visits scheduled (Dunham, 2022). Electronic health records (EHRs) were thought to be a solution in alleviating the administrative burdens of healthcare and medication management. Furthermore, EHRs have not only simplified the prescription process but also have eased communications in this area leading to more prescriptions being initiated and written overall.[6] However, some studies have suggested that it contributes to exhaustion and fatigue.

There are a variety of barriers to effective medication review processes. These can be related to patient, physician, resource, regulation, qualification, and remuneration barriers (Assab et al., 2022). Additionally, poor documentation of drug changes, automated prescribing practices, dependence on patient requests, and ignorance of the medical notes are also problematic (Alghadeer et al., 2021). Patient-related challenges are a large part of issues stemming from a medication review, including knowledge of personal medication use and overall health literacy. Other challenges come from nonadherence to prescribed medications. For example, approximately 4.3 billion prescriptions are written every year, but fewer than half are taken as prescribed.[7] Proper adherence to medication regimens includes having an uninterrupted supply. Taking more than one medication at a time and keeping track of varying refill dates can present a burden.

Empirical evidence agrees that a standardized protocol must be adopted to avoid medication safety issues. A medication review can be performed by itself or with other interventions, such as patient education. Multiple trials have concluded that computerized support can greatly diminish errors in prescribing practices.[5] However, empirical evidence suggests that involving pharmacists in the medication review process allows for greater accuracy, improved efficiency, reduced error rates, and increased patient satisfaction(Alghadeer et al., 2021; Bhakta et al., 2022).. Regardless of the implementing party, strategies and interventions are vital in reducing potentially inappropriate medication prescribing in various settings.[9]

Given the burden of delivering care in a high-quality setting, strategies should be as simplistic as possible and not create additional workflows. Therefore, this quality improvement project aimed to incorporate simple medication review protocols into patient care, a standardized rooming experience, and updated medication refill procedures to lessen the burden of refill requests on a primary healthcare facility, and to improve patient and healthcare staff safety and satisfaction in the USA.

The remaining paper will discuss the methods, results, discussion and concluded with research implications.

2. Methods

This quality improvement project aimed to improve the efficiency of the medication review process in one primary care practice in the United States (U.S.) with over 16,000 encounters a year. An interdisciplinary team that included representatives from clinical operations, physician leadership, nursing, clinical pharmacy services, and patient access was created to map out the medication refill process already employed. For this, lean process was used which is a process improvement approach and evidence-based method for improving production capacity, decreasing costs, increasing satisfaction, and reinforcing leadership.[10] While this framework has been used extensively in the manufacturing sector, research suggests that when applied to healthcare, errors become more visible, increasing response and making them less frequent.[11] Therefore, the Lean framework was deemed essential to identifying possible areas in the medication refill process that could be improved.

2.1. Data Collection and Settings

After defining the medication refill process, challenges were analyzed including patient, systematic, and provider-related etiologies. Data were collected from November 1, 2021, to November 2, 2022, from the practice's Nextgen EHR system. The names of highly prescribed medications and the frequency of these medications as being re-prescribed were quantified. The interdisciplinary team met to discuss opportunities for improvement that could be easily implemented by the healthcare team and were customizable along with the rapid evaluation and feedback inherent to all quality improvement projects.

2.2. Sample and Sampling Technique

Convenience sampling was used for this study. The sample included all phone calls received by the primary care practice located in Texas, requesting medication refills from November 1, 2021, to November 2, 2022 (n = 4,029) at a healthcare practice with over 16,000 encounters a year for primary care services. The quality improvement

project only involved participants ordinarily seen by this practice. No external recruitment of participants occurred. Since this was a quality improvement project, IRB approval was not required.

2.3. Data Analysis

After determining the number of refill requests received by the practice during the study period, the number of related visit encounters was determined. The percentage of refills per encounter was calculated monthly, and temporal trends were assessed to determine if refill call volumes decreased post-quality improvement project implementation. Data were analyzed via IBM SPSS v.29. To ascertain if any statistically significant differences occurred in refill calls pre- versus post-project implementation, *t*-tests were used. All analyses were calculated with a 95% confidence interval and deemed statistically significant with a *p*-value equal to or less than 0.05.

3. Results

This study has analyzed potential challenges, suggested much needed improvements and identified the significance of this project with statistical analysis.

3.1. Analyzed Potential Challenges

The challenges analyzed by the interdisciplinary team included patient, systematic, and provider-related etiologies. For example, patients did not typically know how many medication refills remained on their current prescription, annual visits were completed without identifying their need, and patients could not operate patient portal technology for refill requests. Moreover, providers had difficulty identifying the medication refill needs during encounters due to inaccurate medication lists documented in the EHR. Furthermore, the EHR system could not support automated reminders for refills, medications due to be refilled were often overlooked during rooming, appointment reminders were made without instructing patients to bring medication bottles, and medication reconciliation needed to be consistently and comprehensively completed.

3.2. Needed Improvements

The interdisciplinary team decided upon several different simple improvements. Appointment reminders and confirmations included patient instructions to bring medication bottles to appointments. Clinic staff was trained on a standardized rooming experience with an enhanced emphasis on medication review. Practitioners inquired about medication bottles brought to the appointments. Furthermore, after identifying the high-frequency medications (Table I) most sought-after in refill requests, the primary care practice's medication refill procedure underwent revision, which was implemented by the nursing staff.

3.3. Statistical Analysis

During the study period, a total of 4,029 refill calls were included. There was a mean of 309.92 (SD = 51.87) refill calls received monthly, ranging from 256 to 408. There were more refill calls received before the implementation of the quality improvement project (M = 391, SD = 23.64) than after (M = 285.60, SD = 24.80), a statistically significant difference, M = 105.40, 95% CI [69.76, 141.04], $t(11) = 6.510$, $p < .001$ (Figure 1).

4. Discussion and Conclusion

The findings from this quality improvement project support the necessity of standardized protocols in a medication review and refill processes in primary care settings. In addition, post-implementation of the project, the number of refill calls significantly decreased, reducing the workload for healthcare professionals and potentially leading to improved patient safety and satisfaction.

One of the significant findings of this study was the decrease in the volume of refill calls after the project's implementation. This result supports existing research that suggests standardized procedures in a medication

review and refill processes can reduce the burden on healthcare professionals and potentially improve patient safety and satisfaction (Alghadeer et al., 2021; Bloomfield et al., 2020; Rantsi et al., 2022). The project introduced a systematic approach that included patient education, a standardized rooming experience, and an updated medication refill procedure, all of which aimed at improving the efficiency of medication management.

The findings align with earlier studies that emphasized the role of pharmacists and computerized systems in reducing errors in prescribing practices (Alghadeer et al., 2021; Bloomfield et al., 2020) . In this project, the expertise of an interdisciplinary team was used, including clinical pharmacists, to revise the primary care practice's medication refill procedure. This approach could help bridge the medication management gap, a concept supported by the literature that advocates for a multidisciplinary approach in primary care settings.[8]

The decrease in refill calls post-implementation suggests that patients may have better understood their medication regimens and refill needs, possibly due to the added emphasis on patient education. This could lead to better medication adherence, which is crucial given that nearly half of all prescriptions are not taken as prescribed.[7] Furthermore, by asking patients to bring their medication bottles to appointments, healthcare professionals could reconcile their medications more accurately, reducing the risk of medication errors.

However, unexpected challenges encountered during this project included technological limitations and inaccurate medication lists in EHR. These findings align with previous literature that pointed out the complexities associated with EHR systems and the potential for these to contribute to physician burnout.[6] While EHR systems were initially expected to alleviate the administrative burdens in healthcare, they have sometimes been found to introduce new challenges (Dunham, 2022). This highlights the importance of ongoing quality improvement initiatives and constant adaptation to emerging issues.

On the other hand, this study reflects a few limitations inherent to all quality improvement projects, such as sustainability in the project, lack of buy-in from all involved, and resistance to change. However, the areas for improvement were acknowledged and created by a diverse team in which workflow was immediately impacted. Increasing ownership among the team could lead to long-term sustainability. Furthermore, confounding factors contributing to lower volumes of refill requests were not ascertained during this project, for instance, the entry and exit of patients into and from the practice. Therefore, this study cannot provide causation.

A notable decrease in refill calls post-implementation indicates a positive impact and significance of this quality improvement project. It is worth noting that the effectiveness of such interventions could vary across different settings, largely dependent on factors like available resources, staff training, and patient population characteristics. Therefore, future studies should consider investigating the applicability of similar interventions in different healthcare settings and evaluating their long-term effects.

In conclusion, this quality improvement project demonstrated the positive impact of standardizing the medication review process in a primary care setting. By focusing on patient education, standardizing the rooming experience, and updating the medication refill procedure, we observed a significant reduction in refill calls, suggesting improved operational efficiency and potentially leading to enhanced patient safety and satisfaction. This project underscores the critical need for standardized protocols in medication management and the importance of a multidisciplinary approach in primary care settings. Future efforts should address the challenges associated with EHR systems and continue to innovate and improve medication management procedures.

4.1. Research Implications

The results of this study can be used in healthcare practices of all sizes and suggest that solutions to increase patient safety in prescribing practices do not need to be overly complicated or increase the workload of already overburdened staff members. It is reasonable to consider more low-cost interventions. However, further research is required to improve prescribing practices and realize their full effect on the health and safety of patients and practitioners.

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Table I: High-Frequency Medications Added to Refill Procedures

Sr. No.	High-Frequency Medications Added to Refill Procedures	Sr. No.	High-Frequency Medications Added to Refill Procedures
1	ACE-I/ARB Medications (-prII/-sartan)	11	Dipeptidyl Peptidase 4 Inhibitor Medications (-gliptin)
2	Alpha Blocker Medications (-azosin)	12	GABA Analog
3	Antihistamine Medications (-itidine/-ine)	13	GLP-1 Receptor Agonist Medications (-glutide)
4	Respiratory Inhalers (SABA, LABA, ICS, Anticholinergics [ACH])	14	Leukotriene Receptor Antagonist (-lukast)
5	Beta Blockers (-olol)	15	Nasal Corticosteroids (-asone/ -onide/ -olide/ -olone)
6	Biguanide Medications (i.e. metformins)	16	Omega 3 Fatty Acids (EPA/DHA)
7	Calcium Channel Blocker Medications	17	Insulin Medications
8	Diabetic Supplies	18	Proton Pump Inhibitor Medications (-razole)
9	Diuretic Medications (-thiazide/-semide)	19	Sodium-Glucose Cotransporter 2 Inhibitor Medications (-gliflozin)
10	Selective Serotonin Reuptake Inhibitors (SSRI)		

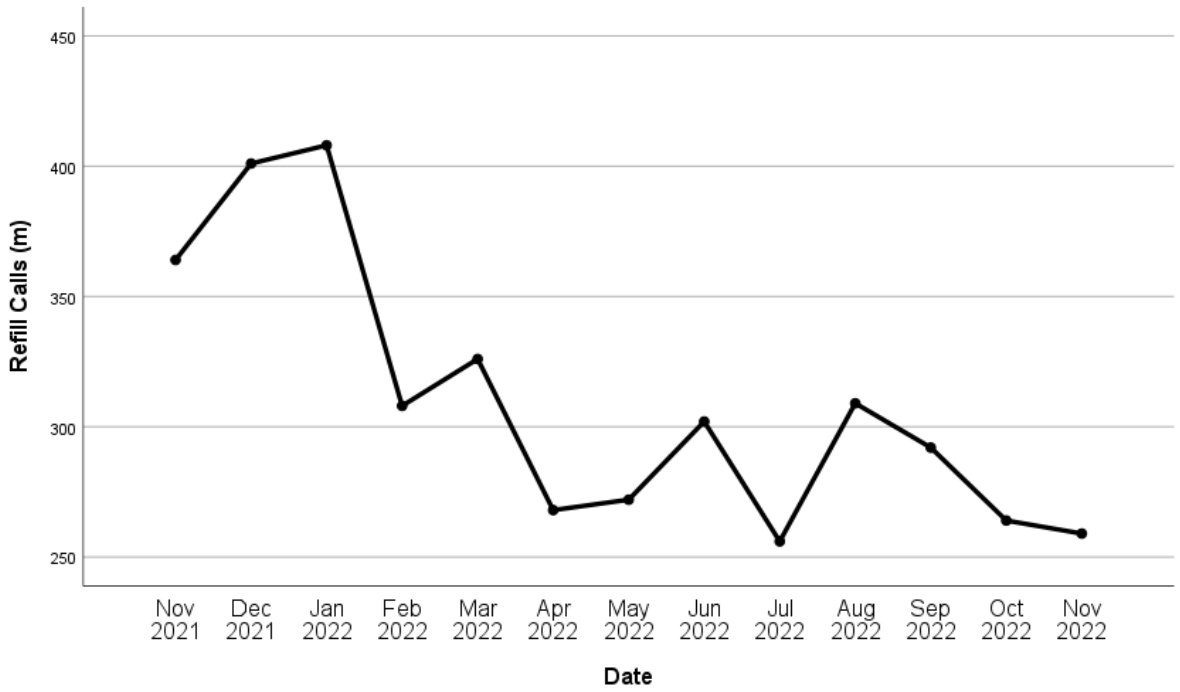

Figure 1: Mean Number of Refill Calls Received per Month

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The Impact of Postpartum Mothers' Stress and Motivation on Breastfeeding Practice

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Abstract
Stress in postpartum mothers affects the production and pattern of breastfeeding. Postpartum mothers with high stress levels will have low self-efficacy, which then affects the breastfeeding pattern of their babies. This study aimed to determine the effect of postpartum mothers' stress levels on breastfeeding practices. This research method uses a correlation study through observation or data collection at one time (point time approach)—a sample of 80 mothers 1-6 weeks postpartum. Data was collected with the DASS (Depression Anxiety Stress Scale) questionnaire and breastfeeding. The research location is PMB East Cilendek and Tanah Sareal, Bogor City. The place was chosen because the failure rate of exclusive breastfeeding is high in that area. The independent variables in the study were postpartum maternal stress, motivation, and health education. The independent variable is breastfeeding in infants. Data analysis used the Lambda contingency coefficient test. Stress in postpartum mothers significantly affects the pattern of breastfeeding in infants. The confounding variables in this study were the motivation to breastfeed and the health education about breastfeeding that mothers had received. For this reason, health workers must be able to educate families, especially husbands, so that they can provide adequate social support to reduce stress on postpartum mothers so that the process of breastfeeding babies can run well.

Keywords: Postpartum Stress, Breastfeeding, Motivation

1. Introduction

Postpartum is a critical period in the transition of a mother's life, marked by several physical and psychological changes that begin after delivery up to 6 weeks. In this situation, a mother needs guidance from a health worker because she has a double task: meeting the needs of herself, her family, and her baby (Dodou et al., 2016). Lack of knowledge and the ability of mothers to deal with the post-partum period can result in fatigue. Yet, according to Reitmanova and Gustafson, fatigue in the post-partum period will cause anxiety (Reitmanova & Gustafson, 2008). According to the research results of Liabsuetrakul, Vittayanont, and Pitanupong, stress that occurs in the mother, lack of a good support system, and lack of knowledge can trigger the occurrence of *post*-partum *blues* and other puerperal complications (Liabsuetrakul et al., 2008). The research is in line with McCarter Spaulding's study,

which stated that post-partum mothers, especially primiparas who experience ongoing confusion in self-care in the post-partum period, are likely to develop post-partum depression (Mccarter-Spaulding et al., 2016).

The post-partum period is divided into 3: the post-partum period (*immediate post-partum*), the *early post-partum* period, and the *late post-partum* (Mccarter-Spaulding et al., 2016). During *early post-partum*, mothers already desire to take care of themselves and their babies and are allowed to stand and walk for self-care. Post-partum care is essential because, during the post-partum period, there are often deaths in the mother caused by various problems such as bleeding and infection; this can occur due to poor post-partum care (Herlina, 2011). The initial period after giving birth for a woman is generally the happiest event, especially if the child is born as expected. Few women experience the same thing and tend to experience harrowing events full of challenges and anxiety (Palupi, 2020).

Women who fail to adjust to biological, physiological, or psychological changes, including role changes, tend to experience emotional problems after childbirth. Psychological issues that often occur in post-partum mothers include post-partum blues/maternity blues, post-partum depression to delusional and hallucinating psychotic disorders. This problem can also be experienced by fathers (husbands or partners of women who give birth), although its occurrence is rarer and has not been studied. Several studies have concluded that post-partum depression can affect the mother's social life, professional skills, and mother-child influence which can be harmful (Erdogan, 2010).

Post-partum depression is defined in the International Statistical Classification of Diseases (ICD-10) as mental and behavioral disorders that occur after six weeks of delivery (WHO, 2007). Clinically, the symptoms of post-partum depression are similar to the criteria for diagnosing depressive disorders in general, namely: lack of enthusiasm in carrying out activities, changes in body weight and appetite, insomnia and even hyper insomnia, anxiety, psychomotor slowness, constant feeling tired and lacking energy, as well as features others that generally appear in those who suffer from depressive disorders. Women who suffer from post-partum depression experience symptoms in the first year after delivery; the impact is that it can affect the quality of life of both mother and baby, infant development, and the mother's inability to deepen parenting skills (Erdogan, 2010).

The prevalence of post-partum depression worldwide varies from 6.5% to 15% for one year after delivery (Leahy-Warren et al., 2011). The prevalence of post-partum depression in developing countries ranges from 2% -74%, with the most significant prevalence in Turkey (Forte Camarneiro & de Miranda Justo, 2020). Research conducted in Brazil states that the prevalence of post-partum depression increases every year. The predictor factor is the mother's lack of understanding to check the condition of herself and her baby so that screening and prevention efforts can be carried out. In Denpasar, the prevalence of post-partum depression reaches 20.5%, with risk factors including sociodemographic, obstetric, and marital factors. Based on the West Java Health Profile in 2012, it is known that in Bogor Regency, as many as 23 post-partum mothers died, even though as many as 87.4% of mothers received post-partum services from health personnel (Jabar, 2017).

According to Notoatmodjo, health behavior is formed by three factors: predisposing, supporting, and driving factors. Predisposing factors manifest in knowledge, attitudes, beliefs, beliefs, and values influencing health behavior. Supporting aspects embodied in the physical environment, availability or unavailability of health facilities or facilities. The third factor is the driving factor manifested in the attitude and behavior of health workers or other officers, which is a reference group for community behavior (Notoatmodjo, 2012). Does the stress felt by the mother affect breastfeeding in the baby? Based on the background above, this research is interested in examining "The Effect of Postpartum Mother's Stress on Breastfeeding in Babies in Bogor City."

2. Method

This research is an observational study using a cross-sectional, namely the measurement of independent and dependent variables carried out in the same group simultaneously. The study was conducted on postpartum mothers 1-6 weeks postpartum at the Independent Midwife Practice (PMB) in East Cilendek and Tanah Sareal, Bogor City. The location was chosen because, in that area, many postpartum mothers still fail to give exclusive

breastfeeding. The research is planned to be conducted in June-November 2020. The samples in this study were postpartum mothers in PMB Cilendek Timur and Tanah Sareal, Bogor City, who met the inclusion and exclusion criteria. The estimated sample size is 80 people.

The sampling technique was carried out by accidental sampling. Each sample must meet the following criteria: the baby was born alive, the mother and baby were not sick (based on the midwife's examination), and the mother had no dysfunction in one or more of her senses. The exclusion criteria were that both the toddler and the mother experienced severe illness while the research was still in progress, a doctor diagnosed the mother as having a mental disorder, and the baby did not live or be cared for by the mother. The data needed in this study are primary data obtained directly from the results of filling out a questionnaire using a stress level questionnaire and breastfeeding. Data on postpartum mothers were obtained from the Independent Midwife Practice, Bogor City. Samples were taken by accidental sampling technique up to 80 postpartum mothers.

Data collection was carried out after the 7th day because, at that time, the mother was psychologically no longer focused on herself (Notoatmodjo, 2012). And at that time, mature milk has been formed, and the newborn's weight loss usually returns to its initial weight. Data collection was carried out when the mother was in control; the enumerator inputted the data online via the Google form. Retrieval of research data using a questionnaire consisting of the following sub-sections: Questionnaire A is the first instrument filled in by the sample in the form of questions about the sociodemographic characteristics of the respondents, including age, parity, culture, education, and occupation. Stress on post-partum mothers is an instrument used in previous studies, namely DASS 21 (Price et al., 2021).

The validity test in this study used the *Rank Spearman*. The questionnaire/observation sheet is valid if the item has an r>0.3. While the reliability test was carried out using the *Cronbach Alpha formula.* An instrument can be reliable if it has a reliability coefficient or *alpha* greater than 0.05 (Dahlan, 2019). Univariable analysis was carried out to describe each variable measured in the study by looking at the frequency distribution of all variables and how each variable varied. Univariable analysis was carried out to describe the frequency and proportion of the various variables studied, both the independent and dependent variables. To analyze the stress level of postpartum mothers on breastfeeding patterns using the Lambda contingency coefficient test.

3. Results

Data collection was started by testing the validity and reliability of the research questionnaire on 30 respondents. As a result, five questions in the questionnaire were declared invalid; then, improvements were made to the questions. Furthermore, data collection has been carried out since September 2020 on 100 postpartum mothers. The sampling technique was carried out accidentally when the control mother went to BPM (7th day), who met the inclusion and exclusion criteria.

3.1. Subject Characteristics

Most subjects had high school and tertiary education, worked as housewives, had first children, received information about exclusive breastfeeding from health workers, had a household income above the minimum wage, were aged 20-35, and experienced moderate stress. The characteristics of the research subjects can be seen in Table 1 below:

Table 1: Characteristics of Research Subjects

Variable		N (80)	(%)
Education	Primary	11	13.8%
	Junior	9	11.3%
	Junior High	30	37.5%
	University	30	37.5%
Occupation	Housewive	50	62.5%
	Employed	30	37.5%
Parity	Primi	45	56.3%

Variable		N (80)	(%)
	Multi	35	43.8%
Breastfeeding Health Education	No	7	8.8%
	Yes	73	91.3%
Wedge	< UMR (4,1 million)	30	37.5%
	>= UMR (4,1 million)	50	62.5%
Age	<20 years	5	6.3%
	20-35 years	60	75.0%
	> 35 years	15	18.8%
Stress level	Normal	22	27.5%
	Mild	23	28.7%
	Moderate	35	43.8%
Diet Practice	Poor	19	23.8%
	Good	61	76.3%
family support	Poor	40	50.0%
	Good	40	50.0%
Breastmilk production	Poor	37	46.3%
	Good	43	53.8%
Breastfeeding practice	Poor	37	46.3%
	Good	43	53.8%
breastfeeding motivation	Poor	41	51.2%
	Good	39	48.8%

3.2. Results of Bivariable Analysis of Factors Affecting The Breastfeeding Practice

Analysis showed that the confounding variables in this study were Health education about breastfeeding from health workers and motivation to breastfeed. In addition, it is also known that the stress level of postpartum mothers significantly affects the breastfeeding pattern.

Table 2: Bivariable Analysis of Factors Correlating to Breastfeeding

Variable		Breastfeeding Practice		Total	R	P
		Poor	Good			
Family Support	Poor	23	17	40	0.225	*0.165
	Good	14	26	40		
Total		37	43	80		
Education	Primary	7	4	11	0.073	**0.667
	Junior	2	7	9		
	Junior High	15	15	30		
	University	13	17	30		
Total		37	43	80		
Occupation	Housewive	23	27	50	0.013	*0.954
	Employed	14	16	30		
Total		37	43	80		
Parity	Primi	19	26	45	0.014	*0.866
	Multi	18	17	35		
Total		37	43	80		
Breastfeeding Health Education	No	7	0	7	0.507	*0.004
	Yes	37	36	73		
Total		37	43	80		
Wedge	< UMR (4,1 million)	13	17	30	0.094	*0.684
	>= UMR (4,1 million)	24	26	50		
Total		37	43	80		
Age	<20 years	1	4	5	0.260	**0.281
	20-35 years	28	32	60		
	> 35 years	8	7	15		
Total		37	43	80		

Variable		Breastfeeding Practice		Total	R	P
		Poor	Good			
Mother Feeding Practice	Poor	10	9	19	0.018	*0.818
	Good	27	34	61		
Total		37	43	80		
Breastmilk Production	Poor	20	17	37	0.081	*0.621
	Good	17	26	43		
Total		37	43	80		
Breastfeeding Motivation	Poor	26	15	41	0.333	*0.042
	Good	11	28	39		
Total		37	43	80		
Stress	Normal	5	17	22		
	Mild	10	13	23	0.523	**0.001
	Moderate	22	13	35		
Total		37	43	80		

*Lambda correlation test **Gamma correlation test

4. Discussion

Both provide nutrition, share the workload and handle difficulties during breastfeeding. Even postpartum mothers need support from the people closest to them. Husband and family support helps the mother overcome problems adjusting to a new role. Most respondents can control their emotions or get angry when they experience problems. Anger due to intractable issues was experienced by at least the respondents in the postnatal period (Ulfa & Setyaningsih, 2020).

Breastfeeding problems often occur in the few days after delivery. The mother feels anxious because the milk is not flowing smoothly, and the milk that comes out is small, so she worries that the baby will not be complete. This anxiety can be overcome if the mother understands the physiology of lactation. Breast milk typically comes out 2-3 days after delivery, and the more frequent breastfeeding, the more milk will be produced. This understanding is often ignored when the mother is worried and there is encouragement from her husband or family to give formula milk to the baby.

There are still 20 subjects (25%) with junior high school education and below. Education, according to Notoatmodjo, will affect one's knowledge and mindset (Notoatmodjo, 2012). As many as 45 people (56.3%) of the research subjects were primi. Primi para is people giving birth or having children for the first time. According to Aprihastiwi, parity positively influences one's experience; mothers with children will be motivated to exclusively breastfeed their second child because mothers breastfeeding are inspired by efforts to breastfeed their previous children (Aprihastiwi, 2015). As many as seven people (9%) subjects have not received health education regarding exclusive breastfeeding. According to Ryadi et al., the source of information is essential. The results of their research show that the source of information and the health information obtained will affect the nutritional condition of children (Riyadi et al., 2011). In other words, it also influences how to provide proper nutrition to children, including exclusive breastfeeding. The study results also showed that thirty people (37.5%) earned income below the minimum wage.

Most (75%) of the research subjects were aged 20-35. The older woman has an optimally developed maturity level. They have more experience in daily applications, strength in thinking, and are not easily tempted by wrong information such as giving formula milk; this situation causes mothers to have a desire or high motivation to provide exclusive breastfeeding to their babies (Mizrak Sahin et al., 2019). This statement follows the results of this study that the mother's motivation in the high category was mostly in respondents with an age range of 20-35, namely 32 people (40%). As many as 19 postpartum mothers (23.75%) had poor eating patterns, including not eating fruit or vegetables daily and not drinking enough water. As many as 37 people (46.2%) of research subjects experienced less milk production. The smooth production of breast milk can be influenced by psychological stress. As was the result of Sari's research, which stated that there was a significant effect between psychological stress and the smooth production of breast milk in primiparous mothers who breastfeed (Puspita Sari et al., n.d.).

Forty-one people (51.25%) of research subjects had less motivation to breastfeed. Motivation is a person's strength or energy to raise persistence and enthusiasm in an activity. Research states that the factors influencing motivation are a person's level of education, knowledge, and economic status. Good motivation can be obtained through health education. The combination of planned learning experiences based on sound theory provided by individuals, groups, and communities can offer the opportunity to acquire the information and skills needed to make quality health decisions. The material or message and the method conveyed must be considered in providing health education.

From the results of the study, there were 22 people (27.5%) who did not experience stress (normal), 23 people (28.7%) with mild stress, and 35 (43.75%) people who were moderately stressed. According to Daima's research, mild stress lasts a few minutes or several hours. The condition of mother feels anxious because she has difficulty breastfeeding. Moderate stress lasts longer, from a few hours to a few days, for example, when the mother feels guilty for the baby because there is little milk for several days. Severe stress occurs because mothers feel anxious, depressed, often angry, and have health problems in breastfeeding. This condition lasts for several weeks (Ulfa & Setyaningsih, 2020).

The results showed that breastfeeding mothers with mild stress are caused by feeling angry, anxious, and depressed due to something happening while breastfeeding or caring for a child. This result follows Roesli's opinion that discomfort comes from something unexpected during breastfeeding, such as heartburn because the uterus contracts to return to its original state, swollen breasts, and painful stitches (Roesli, 2012). According to Daima, the moderate level of stress experienced by mothers is the feeling of not being able to breastfeed or care for the child, experiencing breastfeeding difficulties, and feeling unable to cope. This condition is mainly caused by less milk production that does not even come out, causing guilt for not being able to breastfeed the baby. Stress in nursing mothers occurs due to discomfort in breastfeeding and caring for themselves and their babies. This condition arises because the mother feels unable to complete the things that must be done. The situation will become more severe if the mother cannot overcome the difficulties that are piling up (Ulfa & Setyaningsih, 2020), especially if the mother does not get adequate support from the surrounding environment. The results showed that lack of support and stress during the perinatal period could put mothers at risk for postpartum depression (Recto & Champion, 2020).

Mothers who do not experience stress will feel happy breastfeeding their babies and will not have significant problems with breastfeeding. Good psychological conditions encourage mothers to breastfeed their babies so that the hormones that play a role in milk production increase because the baby's suction when breastfeeding stimulates milk production. Mothers who experience emotional disturbances can interfere with the let-down reflex process so that less milk is released. At the same time, breast milk creates a feeling of laziness breastfeeding and causes discomfort to the mother, which can trigger stress. Research shows that parenting stress is associated with lower parental sensitivity to their children (i.e., parental responsiveness), negatively affecting child outcomes (Kim et al., 2021). The study results show that the mother's stress symptoms are influenced by how the functioning of the family runs in the family (Qin et al., 2022).

As many as 37 mothers were included in the category of poor breastfeeding patterns. Meanwhile, 43 people (53.75%) were mothers with a good breastfeeding pattern category. For mothers in the good category, one of the indicators is giving only breast milk until data collection (7th day). As many as 37 mothers had already given formula milk, plain water, or honey to their babies' lips. Exclusive breastfeeding only gives breast milk to babies without additional food or other drinks, including water, until the baby is six months old. Exclusive breastfeeding benefits the mother and baby, such as protecting the baby's digestive tract and preventing diarrhea and infection. Breastfeeding protects mothers against breast and uterine cancer risks and provides contraceptive benefits for six months of breastfeeding (WHO, 2016).

Tactile nerve endings in the nipples receive stimulation when the mother is breastfeeding. This stimulation is carried to the hypothalamus at the base of the brain, then stimulates the anterior pituitary to secrete the hormone prolactin into the blood, spurring the epithelial cells (alveoli) to produce breast milk. The secretory activity of the mammary glands is influenced by the psychological psychology experienced by the mother (Roesli, 2012).

4.1. Influence between Breastfeeding Motivation and Breastfeeding Patterns

From Table 2, it is known that motivation in mothers to breastfeed has a significant correlation with breastfeeding patterns, with a correlation value of r 0.333 and a p-value of 0.042. According to Dahlan, the value of r 0.20-0.399 can be interpreted with a weak correlation. This situation happens because many other factors could have a stronger correlation with the practice of breastfeeding. The direction of the correlation is positive or unidirectional, so the greater the value of the mother's motivation to breastfeed, the better the breastfeeding pattern will be. It can be concluded that a mother's good self-confidence to produce enough breast milk to meet her baby's needs will be an essential basis for her success in breastfeeding. When a mother has strong motivation or encouragement, the mother will have an excellent ability to breastfeed. There is a significant relationship between the motivation and independence of postpartum mothers in self-care during early postpartum (Safitri & Cahyanti, 2016). Research shows that mothers who exclusively breastfeed their babies are more motivated than those who partially breastfeed. In addition, adult age, higher education level, non-smoking status, and breastfeeding support positively influence breastfeeding motivation (Mizrak Sahin et al., 2019).

This study follows the theory of Notoatmodjo, which says that motivation is the driving force or impetus to do something that comes from (intrinsic) motivation within oneself due to awareness of the importance of something. Supporting research shows that the mother's beliefs and motivation are factors that are influential in breastfeeding behavior (Listyaningrum & Vidayanti, 2016). Mothers with good motivation and self-confidence will be better able to provide exclusive breastfeeding to their babies. They state that the mature woman has the level of maturity to develop optimally, including experience in daily applications. They have strength in thinking, so one is not easily tempted by wrong information, such as giving formula milk; this condition causes mothers to have a high desire or motivation to provide exclusive breastfeeding to their babies.

4.2. The Effect of Health Education on Breastfeeding Practice

As seen in Table 2, the correlation value between Mother's Health Education about Breastfeeding and the stress level is 0.507 with a p-value of 0.004. According to Dahlan, the correlation value is included in the medium category, with a positive direction. This result is unidirectional; the greater the value of Health Education, the better the breastfeeding practice. This condition follows the results of Lestari's research, which states that overall, it can be concluded that there is an increase in the level of knowledge, ability, and motivation after being given health education using audiovisual media without using audiovisual media. After receiving health education using audiovisual media, primiparas' knowledge, abilities, and motivation became higher than those given health education without audiovisual media. It can be concluded that health education using audiovisual media effectively increases primipara breastfeeding knowledge, knowledge, abilities, and motivation. Therefore, it is recommended that health workers be able to provide health education about breastfeeding using audiovisual media, especially for primiparas because it is more effective than delivering health education without audiovisual media. Lestari's research showed a significant increase in the experimental group in the level of knowledge by 28% (pv=0.00), the ability to breastfeed by 41.33% (pv=0.001), and the motivation to breastfeed by 19.34% (pv=0.033).(lestari et al., 2014)

Listyaningrum and Vidayanti, in their research, said that there was an influence on mothers' motivation in exclusive breastfeeding. Motivation is one factor that influences mothers in giving exclusive breastfeeding; motivation is a state of a person's personality that encourages an individual's desire to carry out certain activities to achieve goals (Listyaningrum & Vidayanti, 2016). Ribek, in his research, said that every mother must have the drive, desire, and ability to breastfeed exclusively (Ribek & Kumalasari, 2020). Health education is one of the efforts to increase mothers' motivation to give exclusive breastfeeding. Health education combines planned learning experiences based on sound theory that can provide individuals, groups, and communities with opportunities to acquire the necessary information and skills. The research results by Lestari, Ameli, and Rahmalia recommend that health workers provide health education about breastfeeding using audiovisual media to increase knowledge, skills, and motivation to breastfeed (Astuti et al., n.d.).

4.3. The Influence of Stress Levels on Postpartum Mothers and Breastfeeding Practice

The stress level of postpartum mothers in this study has a moderately negative and significant correlation to breastfeeding patterns, with a correlation coefficient of r -0.523 and a p-value of 0.001. This value indicates that the stress level correlates with the breastfeeding pattern. The higher the level of stress experienced by the mother, the less good the mother does in the practice of breastfeeding. The postpartum period is a difficult time for developing severe mood disorders. The mother will feel mentally disturbed at this time even though no complications occur during pregnancy and the delivery process. Most women experience changes after giving birth in their physiological, psychological, and social aspects; some suffer from mild to severe mental disorders (Erdogan, 2010)(Guan et al., 2021).

Three problems can occur now: postpartum blues, postpartum depression, and postpartum psychosis. Each problem has a different prevalence, clinical symptoms, and management. Counselling and social support Providing counselling to couples and families is informational support, namely to increase the knowledge of partners and families about the incidence of depression in mothers. Thus, the husband and family will put more effort into supporting the mother during the postpartum period or parasites that cause disease (Potter & Griffin, 2012). Physiological stress is caused by physiological processes in the body that become abnormal, namely structural, tissue, organ, or systemic disturbances. Stress in the process of growth and development occurs due to growth and development disorders from infancy to old age. Psychological or emotional stress is caused by disturbances of interpersonal, social, cultural, or religious influences (Potter & Griffin, 2012).

Based on the results of Suryani's research, it was found that ρ was 0.041, which means there is an influence on the stress level of breastfeeding mothers with breastfeeding in the first month. The odds Ratio (OR) of 9.33 (95% CI = 1.38, 63.20) means that mothers with moderate-to-severe stress levels have a 9.33 greater probability of not breastfeeding in the first month. (Manurung, 2008) Breastfeeding mothers who do not experience stress or experience stress in the mild phase are more likely to continue breastfeeding in the first month. The impact if babies are not breastfed in the first month is believed to be able to increase 1/3 of the incidence of Upper Respiratory Tract Infection (ARI), the incidence of diarrhoea can increase by 50%, and severe intestinal disease in premature infants can increase by 58%. (Kemenkes, 2015) Neonates or newborns who are exclusively breastfed have a lower risk of death from infection in the first month than neonates who are partially breastfed (not exclusively for six months). Effective promotion of early initiation of breastfeeding and exclusive breastfeeding during the first month of life significantly reduces neonatal mortality and morbidity (Khan, J., Vesel, L, Bahl, R., and Martines, 2015).

The percentage of babies receiving exclusive breastfeeding in Indonesia in 2017 was 35.73%, still far below the national target of 80%. (BPS, 2019) According to Puspita Sari's research, as many as 75% of mothers experience stress because breast milk does not come out smoothly. As many as 60% of mothers feel sorry for their children because they are still fussy and cry if they are only given breast milk. A small proportion (20%) obtained information from older people in the village about providing food (bananas, porridge) and thought that giving food to infants aged less than six months had no negative impact on infants (Puspita Sari et al., n.d.).

Stress can affect breastfeeding; for example, mothers experience difficulties at the beginning of breastfeeding, such as fatigue, little milk, sore nipples, and sleep disturbances at night (Susanti, 2014). Stress can affect milk production because it inhibits milk production and eventually results in breastfeeding. Stress affects the continuity of exclusive breastfeeding. The success of breastfeeding affects milk production, while stress can affect milk production. Mothers who experience moderate stress successfully breastfeed because they are motivated to increase milk production. Motivation comes from oneself, the environment, family, and health workers (Elsanti & Isnaini, 2018). Difficulties in adjusting roles after delivery, if proper treatment is carried out after some time, can impact the mother's and her baby's health and well-being. From a few days after delivery until the first month, breastfeeding problems are often experienced.

Stress is a stimulus or situation that causes distress and creates physical and psychological demands on a person. Stress requires coping and adaptation. The body's response can be predicted without regard to a particular stressor

or cause.(Elsanti & Isnaini, 2018) Conditions that require coping and adaptation include the period after childbirth. Anxiety may increase during this period. Mothers experience a unique experience because there is a change in roles and responsibilities, including breastfeeding. The stage of carrying out this role can be a stressor when the mother experiences difficulties and cannot overcome them. Stress is divided into 3 (three) categories: mild, moderate, and severe. *Mild stress* is a stressor that everyone regularly faces, lasting minutes or hours. Moderate stress lasts longer, from a few hours to several days. *Severe stress* is a chronic situation that can last from weeks to years (Potter & Griffin, 2012).

5. Conclusions

Stress levels in postpartum mothers are correlated with patterns of breastfeeding. Motivation and health education about breastfeeding are correlated with patterns of breastfeeding. Health education or counselling is needed to motivate mothers to breastfeed correctly. In addition, cooperation from various parties is required to minimize stress on postpartum mothers so that mothers can breastfeed with the correct practice.

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Informed Consent Statement/Ethics approval: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Health Research Ethics Commitee, Ministry of Health, Bandung Health Polythechnic (No. 15/ KEPK/EC/X/2020). All participants fully informed if the anonymity is assured, why the research is being conducted, how their data will be used and if there are any risks associated.

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