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Under-Two Children Hunger Levels in Indonesia

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Abstract

Objective: To analyze the hunger level of toddlers under 2 years old using the Under-two Children Hunger Index (CHI).

Methods: This study used secondary data from the Indonesian Basic Health Survey 2018. This study focused on the development of measurement for under-two children hunger index (CHI) using six indicators of the prevalence of chronic energy deficiency in pregnant women; the prevalence of risk height of pregnant women; the prevalence of under-two children who never being breastfeed; the prevalence of malnutrition for under-two children; the prevalence of wasting for under-two children; and the prevalence of stunting for under-two children. These six indicators were weighted differently and were calculated using the Principal Component Analysis (PCA) method.

Results: The calculation of CHI using loading factors as weighted indicators has a higher precision with the percentage of 94.12 percent. With a 2018 CHI score of 46.40, Indonesia is at a serious CHI level. From the 34 provinces in Indonesia, 47.06% of provinces are at an extremely alarming level, 8.82% are at an alarming level, 17.65% are at a serious level, 17.65% are at a moderate level, and 8.82% are at a low level. Efforts can be performed by the government to increase the CHI based on the 6 indicators mentioned above.

Conclusion: Based on this analysis, 25 provinces need attention in terms of the CHI level with six, three, and sixteen provinces suffered from a serious, alarming, and extremely alarming levels of CHI, respectively. Nevertheless, CHI is dynamic and should be updated annually to assess the province's achievement in eradicating hunger. This time-series data is very important to evaluate government programs and programs to accelerate the eradication of under-two children's hunger should focus on the six indicators in this study.

Keywords: Stunting, under-two children hunger index, wasting

Introduction

In 2015, all members of the United Nations committed to supporting global initiatives in eradicating poverty, reducing inequality, and protecting the environment. These global commitments produced the Sustainable Development Goals (SDGs) declaration containing 17 Goals and 169 targets that should be achieved in 2030. This paper exclusively focuses on the second goal of SDGs: end hunger, achieve food security, and improved nutrition for all people in Indonesia, especially for those who are poor and vulnerable, including the baby. The measurement of multidimensional hunger at the national, regional, and global levels indicated that all countries over the world have had positive progress in hunger eradication since 2000, but that is still a big problem because 50 countries are still at a serious level of hunger.

To evaluate progress in hunger eradication, International Food Policy Research Institute (IFPRI) released the Global Hunger Index (GHI) report.[1] This yearly report explained hunger and food insecurity in countries

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over the world. GHI is a composite index produced by three dimensions from four indicators with the same weight. The first dimension is inadequate food supply with undernourishment indicator by FAO: the share of the population that is undernourished, whose caloric intake is insufficient. The second dimension is child under nutrition with two indicators which are child wasting and child stunting WHO. Child stunting is the share of under-five children who are wasted with low weight for their height reflecting acute nutrition and child stunting is the share of under-five children who have low height for their age reflecting chronic under nutrition. The third dimension is child mortality, the mortality rate of under-five children in a part of the reflection of the fatal mix of inadequate nutrition and unhealthy environments. This data was released by United Nations Children's Fund.

However, Aiga said that the same weighting method that was used by IFPRI in calculating GHI did not represent the weight for each dimension and indicator. Aiga suggested using different weighting for different dimensions, 2/3 for the first dimension, 2/9 for the second dimension, and 1/9 for the third dimension.[2] Then, Ibok *et al.*[3] developed GHI measurement to measure the vulnerability to the food insecurity index compiling three dimensions from twelve indicators with the same weighting.Some of those indicators also use in global hunger indicators. Whereas, te Lintelo *et al*.[4] measured the Hunger Reduction Commitment Index for a set of developing countries from nine equally weighted indicators.

Hunger is very susceptible for children. Jones, *et al*.[5] research suggests that families that are dealing with negative life, inadequate income, and social support are particularly vulnerable to children's hunger. Children's hunger can be affected by bad parenting style, especially for the 1000 first day of life movement. This period consists of 270 days (9 months) during pregnancy and 730 days (24 months) after the baby's birth. Nutritional problems during this period will cause difficulties in optimizing physical and cognitive development.[6] Age 0–24 months is a critical age for children. In this period, children need sufficient nutrition, not only in quantity but also quality, for achieving optimal weight and height of children. Under-two children's development and growth are determined for great children's development in the future.[7] At this age, under-two children's development and growth can be observed easily because every child has the same development pattern at different velocities.[8]

Children's upbringing in breastfeeding and complementary feeding of the breastfed in the first year of children's life is very important for the development of each child's full human potential.[9] This point of view is the same as Balk *et al*.[10] research to inspect households having children one until three years of age. They concluded that the similarity of the household characteristics is a significant risk factor causing undernourishment, especially in breastfeeding duration and nutritious food. Indonesian awareness of breastfeeding should be increased. In 2018, there were only 67 of 100 babies aged zero until six months who got exclusive breasts. Whereas, Indonesian government regulation number 33 of 2012 concerning exclusive breastfeeding states that every mother should provide exclusive breastfeeding for every baby she had. The center of Data and Information, The ministry of health stated that exclusive breastfeeding is recommended in the first six months of a child's life because breast milk is not contaminated by everything worse for a baby's life and contains many nutrients needed by children at that age.[11]

Insufficient process in breastfeeding and complementary feeding of the breastfeeding for under-two children caused children to live a limited life, such as low height for children's age, slow brain development, and easy to get pain. These characteristics are known as stunting. Stunting is a failure condition in under-two children growth due to chronic malnutrition which has happened for a long time, from infancy until 2 years old. Now, the prevalence of stunting in Indonesia is relatively higher than in other middle-income countries in the world. Although this prevalence decreased in 2018, this prevalence exceeded the WHO stunting threshold amount by 20 points. The prevalence of stunting in 2018 is 30.8% in other words, 31 of 100 under-five children suffered from stunting.[12]

Based on the elucidations above, it concludes that so much research that told about hunger but there are still no studies about the measurement of hunger for under-two children. Is known that hunger in children can be affected by inadequate children up bridging, especially in 9 months during pregnancy and the first 24 months after the baby's birth, so in measuring the level of hunger, it is necessary to include the pregnant women as an indicator to compute the index. Based on these facts,

this study focuses on the development of measurement for CHI using six indicators, they are the prevalence of chronic energy deficiency in pregnant women; the prevalence of risk height of pregnant women; the prevalence of under-two children who never breastfed; the prevalence of malnutrition for under-two children; the prevalence of wasting for under-two children; and the prevalence of stunting for under-two children. These six indicators have different weights which are calculated using the PCA method. The objective of measuring the CHI is to evaluate the performance of all Indonesian provinces to achieve zero hunger. This indicator will be compared with Aiga weighting and IFPRI weighting then will be ranked from the highest index to the lowest one. The CHI measurement is expected to make government intervention can be focused and stay on target.

Methods

This study used secondary data from Indonesia Basic Health Survey named Riskesdas which was conducted in 2018. These data were used to evaluate the achievement of health indicators at the national and provincial levels. The targeted sample is 300.000 households within 30.000 census block-based which had done by Statistics of Indonesia with the Probability Proportional to Size (PPS) method using linear systematic sampling and two-stage sampling.

Indicators and variables that were selected in composing the hunger index for under-two children were based on Global Hunger Index by Concern Worldwide and Welthungerlife and growth and development for under-two children. These indicators were the prevalence of chronic energy deficiency in pregnant women (X_1); the prevalence of risk height of pregnant women (X_2); the prevalence of under-two children who have never been breastfed (X_3); the prevalence of malnutrition for under-two children (X_4); the prevalence of wasting for under-two children (X_5); and the prevalence of stunting for under-two children (X_6). All of these indicators are data at the province level.

After selecting the indicators, their value would be standardized by z-score and distance to scale (0–100). The next step is to determine the weight for each indicator by using the factor analysis method. The data should have multivariate normal distribution tested by the Royston method. Based on Korkmaz's statement, the Royston method is used to determine the distribution of the multivariate data. Royston test shows that the Royston statistical value is 11.2802 and the p-value is 0, 0852. It concluded that the data have a normal distribution.[13]

A weighting method was used to determine the relative importance of the indicators in forming the under-two children's hunger index. Good ridge stated that it was necessary to calculate the weight for each indicator if they have some different indicators to compute an index.[14] The CHI index is constructed as follows:

$$CHI_i = \sum_{i=1}^{34} w_j x_{ji} / \sum_{i=1}^{34} w_j \quad \ldots\ldots (1)$$

Where CHI_iUnder-two children are hunger index for i province and $w_j$are weight for indicator j (a result of loading factor enumeration). Weight enumeration for each indicator used the eigenvalue resulting from the principal component analysis method[15]. It used a maximum factor in the factoring process and the weight for each indicator was the proportion of its eigenvalue to the total eigenvalue. Table 1 below gives information about the weight of the indicators:

In Indonesia, there are 34 provinces. They are classified into 5 categories based on composite cut-off points. The composite cut-off point is calculated as follows:

$$K_j = \sum_{j=1}^{6} w_j c_{jk} \quad \ldots\ldots (2)$$

Where j = 1, 2... 6; k = 1, 2... 34; K_j is the composite cut-off point of indicators and CJK is the standardized value of indicator cut-off point.

The under-two Children Hunger Index scale shows the severity of toddlers under two years old hunger, from low to extremely alarming categories. The first category is for the provinces included with low hunger levels, the second category is for the provinces included with moderate hunger levels, the third category is the provinces with serious hunger levels, the fourth category is the provinces with an alarming level of hunger, and the last category is the provinces with extremely alarming hunger level. It is important to affirm that a province that is identified as having an alarming level of under-two children hunger does not mean that all under-two children are vulnerable to hunger. Then, a province that is identified with a low hunger level of under-two children does not mean that all of the under-two children resist hunger. The smaller index, the lower of under-two children's hunger level.

Table 1 Weight for Each Indicator

Code	Indicator	Weight
X_1	Prevalence of chronic energy deficiency in pregnant women	0.15
X_2	Prevalence of risk height of pregnant women	0.11
X_3	Prevalence of under-two children who never being breastfed	0.44
X_4	Prevalence of malnutrition for under-two children	0.03
X_5	Prevalence of wasting for under-two children	0.08
X_6	Prevalence of stunting for under-two children	0.20

Table 2 Correlation Result between X1, X2, X3, X4, X5, and X6

Indicators	X_1	X_2	X_3	X_4	X_5
X_2	-0.108				
X_3	0.124	-0.029			
X_4	0.403*	0.333**	0.601*		
X_5	0.243	0.345*	0.203	0.530*	
X_6	0.247	0.112	0.311**	0.551*	0.468*

Note: * Significant at the 5 percent level, ** Significant at the 10 percent level

On the other one, the greater index, the more alarming under-two children's hunger levels.

Result

Indonesia has 34 provinces with a 5.4 million population. The result of descriptive analysis from the indicators which is used to compute the under-two children hunger index showed that the average of chronic energy deficiency in pregnant women prevalence and risk height of pregnant women prevalence is 17.98% and 30.94%. These statistics mean that 18 of 100 pregnant women suffer from chronic energy deficiency and 30 of 100 pregnant women have a risk of height. On average, there are 7.81% of under-two children who never breastfed, 4.39% of under-two children suffered from malnutrition, 12.17% of under-two children were wasting, and 4.52% of under-two children were stunting.

Table 2 shows the correlation result among the six indicators composed of under-two children's hunger index. Based on that table, most of all indicators correlate with each other with a positive correlation. However, there are 2 negative correlations, they are the prevalence of chronic energy deficiency to the prevalence of risk height in pregnant women indicator and the prevalence of risk height in pregnant women to the prevalence of under-two children who have never been breastfed.

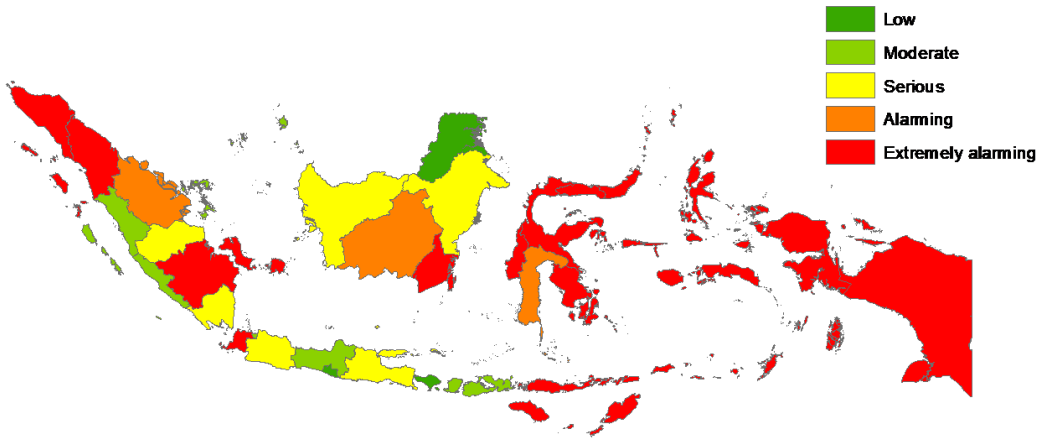

Fig. 1 Under-two Children Hunger Index Map of Indonesia

Table 3 Rank and Score of Under-two Children Hunger Index in Indonesia

Province	CHI_{IFPRI} Score	CHI_{IFPRI} Rank	CHI_{Aiga} Score	CHI_{Aiga} Rank	$CHI_{loading\ factor}$ Score	$CHI_{loading\ factor}$ Rank
Aceh	63.53	32	66.04	33	65.50	30
Sumatera Utara	57.56	29	64.34	32	68.81	32
Sumatera Barat	40.17	10	32.24	7	37.35	7
Riau	41.89	13	42.87	15	48.41	16
Jambi	53.06	23	43.78	16	46.28	14
Sumatera Selatan	49.72	22	47.95	22	56.18	23
Bengkulu	32.65	6	29.90	6	38.55	8
Lampung	38.15	8	34.57	11	43.32	11
Bangka Belitung	43.24	14	50.32	24	56.27	24
Kepulauan Riau	27.08	5	28.81	5	36.61	5
Jakarta	23.55	4	20.74	4	32.75	4
Jawa Barat	37.66	7	32.59	9	40.72	10
Jawa Tengah	40.26	11	32.48	8	36.67	6
Yogyakarta	15.14	1	5.65	1	12.17	1
Jawa Timur	46.11	17	39.43	12	44.86	12
Banten	43.66	15	39.90	13	53.90	20
Bali	18.59	3	16.63	2	23.72	3
Nusa Tenggara Barat	38.48	9	34.04	10	39.24	9
Nusa Tenggara Timur	69.87	33	59.24	28	60.62	28
Kalimantan Barat	46.21	18	44.59	17	45.17	13
Kalimantan Tengah	53.48	24	47.94	21	51.27	18
Kalimantan Selatan	48.16	19	46.44	19	53.74	19
Kalimantan Timur	41.39	12	39.95	14	47.02	15
Kalimantan Utara	16.81	2	18.07	3	23.13	2
Sulawesi Utara	49.50	21	63.87	31	64.51	29
Sulawesi Tengah	48.65	20	45.83	18	55.51	22
Sulawesi Selatan	46.08	16	47.73	20	50.53	17
Sulawesi Tenggara	54.79	27	55.78	26	59.68	27
Gorontalo	58.91	31	63.11	29	56.66	25
Sulawesi Barat	57.62	30	54.25	25	57.71	26
Maluku	77.10	34	89.36	34	84.35	34
Maluku Utara	55.77	28	63.49	30	66.16	31
Papua Barat	54.17	26	58.61	27	70.64	33
Papua	53.73	25	48.15	23	54.29	21

Table 4 Children Hunger Index Scale for Each Method

Weight	GHI Severity Scale				
	Low	Moderate	Serious	Alarming	Extremely Alarming
IFPRI's weight	<31.77	31.78-39.59	39.60-46.85	46.86-53.03	>53.04
Aiga's weight	<27.19	27.20-36.60	36.61-44.04	44.05-50.18	>50.19
Loading factor's weight	<31.76	31.77-40.61	40.62-47.28	47.29-53.71	>53.72

Table 5 The APPER Value and the Accuracy of These Three CHI Calculations

Weight	APPER (%)	Accuracy (%)
IFPRI's weight	14.71	85.29
Aiga's weight	11.76	88.24
Loading factor's weight	5.88	94.12

The next step is doing a CHI calculation using the IFPRI's weight, Aiga's weight, and the loading factor weight.[2] The weight that is used by IFPRI in CHI calculation is $IKB_{IFPRI} = 1/6(X_1 + X_2 + X_3 + X_4 + X_5 + X_6)$ and the Aiga's one is $IKB_{Aiga} = 1/18(X_1 + X_2) + 3/9(X_3 + X_4) + 1/9(X_5 + X_6)$. Whereas, the weight resulting from principal component analysis is $IKB_{loading\ factor} = 0{,}15X_1 + 0{,}11X_2 + 0{,}43X_3 + 0{,}03X_4 + 0{,}08X_5 + 0{,}2X_6$. The result of these three methods is shown in Table 3.

The CHI from these three methods is classified into 5 categories based on the cutting point of each index calculation method. The higher level the higher hunger happened for each province. CHI scale for each method is explained in Table 4. After all of this step, the discriminant analysis method is used to test the accuracy of these three index calculations. Based on that classification, the *Apparent Error Rate* (APPER) is calculated to know about the accuracy of these three index methods(Table 4)

Based on Table 5, the method which is the highest accuracy is the loading factor's weight using the principal component analysis method. The percentage of accuracy is 94, 12% and on the other side, the percentage of the wrong classification is small, which is 5, 88%. These statistics values mean that 32 provinces are classified in the right classification. The APPER value and the accuracy calculation proved that the indicator weight calculated by the loading factor of the component principal analysis method is the best method because the weight of each indicator is different. This method is more objective and conscientious.

Discussion

Based on index calculation using component principal analysis, Indonesia's Under-two Children Hunger Index is 46.40, which stays at a serious level. There are 5 provinces with the lowest score index: Yogyakarta (12.17), Kalimantan Utara (23.13), Bali (23.72), Jakarta (32.75), and Kepulauan Riau (36.61). On the other hand, 5 provinces with the highest score index are Maluku (84.35), Papua Barat (70.64), Sumatera Utara (68.81), Maluku Utara (66.16), and Aceh (65.50). Fig. 1 shows the spread of under-two children hungers in Indonesia.

Of 34 provinces in Indonesia, there are three provinces (8.82%) suffered from a level of CHI that is low, six provinces (17.65%) suffered from a moderate level of CHI, six provinces (17.65%) suffered from a serious level of CHI, three provinces (8.82%) suffered from an alarming level of CHI and sixteen provinces (47.96%) suffered from an extremely alarming level of CHI. All provinces suffering from hunger in under two children are indicated by the prevalence of chronic energy deficiency in pregnant women, the prevalence of under-two children who never breastfed, and the prevalence of wasting and stunting for under-two children are high. The mean prevalence of chronic energy deficiency in pregnant women from all provinces suffering from extremely alarming CHI is 20.8%. It is different than the provinces which have a low and moderate levels of CHI. So, the policies can be focused on chronic energy deficiency in pregnant women. It is very important to reduce hunger both in under-two children and under-five children in Indonesia. For sure, children's growth and development are started when the baby is still in the womb. The result of this research is paralleled with the Balk *et al*.[10]

Another indicator that is very influential for CHI is the prevalence of under-two children who never breastfed with a mean is 9.9%. Breastfeeding is very important to support children's growth and development because it contains nutrition which is very important for the baby. This is paralleled with the previous research stating that the impacts of chronic energy deficiency on a fetus are stunted fetal growth, miscarriage, stillbirth, neonatal mortality, congenital defects, anemia on the infant, asphyxia intrapartum, and low birth weight.[16,17,18,19] The prevalence of wasting and stunting for under-two children will be getting worst if this indicator has never been eradicated. Based on these facts above, the treatment for pregnant women, children lactating, and under-two children malnutrition should be a major concern of the government,

especially in the provinces that are suffering from the extremely alarming level of CHI.

Anyhow, CHI was dynamic and should be updated every year to know about the achievement of every province in eradicating hunger. This time-series data is very important to evaluate government programs. The government can focus on six indicators to eradicate under-two children's hunger. The recommendation for the next research is to add other indicators which could be relevant to CHI. The research suggestion is for the government who can increase the CHI value based on the 6 indicators that were used to calculate CHI. Then, CHI can be guidance in making policy and government programs.

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Mental Health Overview in Bullying Victim Students: A Descriptive Analysis

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Abstract

Objective: To identify the impact of bullying behavior on the mental health of students who are victims of bullying.

Methods: This was a cross-sectional descriptive quantitative study on 105 students in Medan Perjuangan district from November - December 2021. Sampling was performed using accidental sampling techniques on students living in the study area. A questionnaire was used to collect data and analysis was performed using univariate analysis with an estimated value of 95% confidence of 5%.

Results: More than 70% of respondents received some forms of bullying such as body shaming, intelligence discrimination, and parental work shaming, discrimination based on their religion and beliefs, and abusive words. More than 60% of students were also discriminated, ridicule, and subjected to physical violence. About 50% of respondents were also bullied based on their financial, racial/ethnicity, and skin color traits and received physical abused.

Conclusion: There is a link between mental health conditions and bullying behavior in students who are victims of bullying.

Keywords: Battlefields, bullying, college, mental health, student

Introduction

Bullying is bad or deviant behavior because bullying behavior has a serious impact on the mental development of learners. The phenomenon of bullying causes anxiety for the students and parents of learners.[1] Another factor that can cause teens to lack confidence is bullying from friends or their environment. Bullying is aggressive behavior that is done intentionally and occurs repeatedly to attack a target or victim who is weak, easily insulted, and cannot defend themselves.[2]

Bullying behavior has a bad impact on victims of bullying, including Low self-awareness, victims often feeling anxious and even depressed, insomnia caused by pain both physical and psychological, Difficulty Concentrating, insecure, and sustainable meaning that victims of bullying who hold a sense of resentment will potentially become bullying behavior in the future.[3] The main factors causing bullying must be realized by parents to guide their children in the use of media at home. One example of a case of bullying that can be seen in the television media is the mobbing of a student whose perpetrator is the victim of a close friend, a father who beat his son to death and is still a case which we often encounter about bullying, another factor that causes bullying is the strength gap factor that arises from physical aspects, social media access containing embarrassing information, the popularity factor that owned, and the desire to harm others.[4]

The provision of homeroom techniques to adolescents aims to provide views as well as knowledge related to the importance of speaking to someone without harm that leads to bullying, in addition to the formal learning that has been obtained in schools researchers

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want to explore the extent to which students' understanding of bullying as a form of reducing bullying behavior, approaches in homeroom techniques are preventive, i.e. directly related to group members in obtaining information, orientation, on new issues, planning and implementing activities, and activities data collection in terms of future education planning.[5] The results of previous studies state that bullying can affect the confidence of the victim. This requires effort to improve the confidence of those affected by the threat. Self-confidence can be obtained from factors external to the victims of bullying such as the social environment. Forms of influence on the social environment of victims of bullying can be through social support, when the victim of a bully gets high social support from the surrounding environment, they instantly receive help from others in the form of affection, trust, care, gratitude, and positive values.[6]

Indonesia's Child Protection Commission identified cases that led to child protection clusters from 2011 to 2016. KPAI said the number of victims of bullying was above 50 from 2011 to 2016. Lastly, in 2016 the number of victims reached 81 people.[7] The figures were found in cases of bullying in the school environment. For the number of bullies, KPAI got a total of over 40 people. The number of bullies in school environments rose to 93 in 2016. The smaller number of victims of bullying compared to the number of bullies indicates that bullying is done by some people, while not comparable to victims.[8]

The results of the study found that as many as 10–60% of school students in Indonesia, at least once a week get unpleasant treatment from bullies either in the form of non-physical such as scorn, ridicule, exclusion, or in the form of bullying treatment physical harm such as beatings or encouragement.[9] According to the National Center for Educational Statistics says one in five students in the U.S. aged 12 to 18 report having been bullied (20.8%). Cases of bullying in Indonesia often occur in educational institutions. Bullying in educational institutions is referred to as KPAI as a form of violence in schools.[10] According to the Findings of the National Commission on Children's Protection, from 2011 to mid-2014 recorded a total of 369 complaints related to the problem. That's about 25% of the total complaints in the field of education as many as 1,480 cases. This study aims to see or identify images of bullying behavior in mental health events in the district of struggle.

Methods

The study uses descriptive research methods with quantitative approaches, as well as a cross-sectional study design. This research was conducted in Medan Perjuangan district in November–December 2021 with the subject being a person who is a student and active student in his school and university. The sample size taken was 105 students and students who met and lived in the area using accidental sampling.

The data collection technique is to use a research questionnaire by looking for samples of people who are still students who are about 15 to 25 years old and have good knowledge and attitudes about mental health. Research instruments using online questionnaires. The variables measured were student bullying behavior as an independent variable and mental health as a dependent variable. Data analysis techniques use univariate analysis and chi-square bivariate analysis to obtain crude oods ratio as measured by an estimated confidence value of 95% to 5%. Data processed with IBM SPSS Statistics Version 20 application.

Results

Studies were conducted to find out the incidence of bullying on students' mental health. The results of the survey of respondents there are as follows.

Table 1 Characteristics of Respondents

Variable	n=105	%
Gender		
Man	49	46.7
Woman	56	53.3
Age	-	-
15–20 years	79	75.2
20–25 years	26	24.8
Job		
Student	69	65.7
College student	18	17.1
Job seekers	18	17.1
Level of Education	-	-
High School	58	55.2
Diploma	4	3.8
Bachelor	43	41.0
Length of Sleep	-	-
<10 pm	51	48.6
>10 pm	54	51.4

Table 2 Distribution of Bullying Behavior in Medan Perjuangan District

Variable	n=105	%
Often get physically bullied	68	64.8
Often get body shaming bullied	74	70.5
Often get discriminated against intelligence bullied	79	75.2
Often get discrimination from the surrounding environment	64	61.0
Often get bullied from a financial point of view	59	56.2
Often get bullied in terms of parental profession	74	70.5
Often get bullied in terms of race/ethnicity and skin color	54	51.4
Often get bullied in terms of religion and belief	75	71.4
Often get bullied in terms of harsh words	77	73.3
Often get bullied by physical violence	63	60.0
Often get bullied by physically harassed	58	55.2

In Table 1. Based on the characteristics of respondents there were 53.3% of the gender variable that dominates in this study, namely women. Furthermore, in the age range category of 75.2% in the range of 15–20 years. According to job variables, 65.7% of respondents are still students. Furthermore, at the education level, 55.2% of respondents were educated in high school. Lastly, on the variable length of sleep, there were 51.4% of respondents had hours of sleep >10 pm. Factors of mental health that affect the bullying behavior of students.

In Table 2. This shows that more than 70% of respondents get body shaming, intelligence

Table 3 Bivariate Analysis of Bullying Victim Factors to Mental Health Students in Medan Perjuangan District (n=105)

Variable	Mental Health		COR (95% CI)**	P-Value
	Yes (%)	No (%)		
Often get physically bullied	86 (81.9)	19 (18.1)	2.056 (1.476-2.862)	0.000*
Often get body shaming bullied	74 (86.0)	12 (14.0)	2.583 (1.659-4.023)	0.000*
Often get discriminated against intelligence bullied	79 (91.9)	7 (8.1)	3.714 (1.972-6.997)	0.000*
Often get discrimination from the surrounding environment	64 (74.4)	22 (25.6)	1.864 (1.402-2.477)	0.000
Often get bullied from a financial point of view	59 (68.6)	27 (31.4)	1.704 (1.337-2.171)	0.000
Often get bullied in terms of parental profession	74 (86.0)	12 (14.0)	2.583 (1.659-4.023)	0.000*
Often get bullied in terms of race/ ethnics and skin color	54 (62.8)	32 (37.2)	1.594 (1.290-1.969)	0.000
Often get bullied in terms of religion and belief	75 (87.2)	11 (12.8)	2.727 (1.704-4.365)	0.000*
Often get bullied in terms of harsh words	77 (89.5)	9 (10.5)	3.111 (1.816-5.329)	0.000*
Often get bullied by physical violence	63 (73.3)	23 (26.7)	1.826 (1.387-2.404)	0.000
Often get bullied by physically harassed	58 (67.4)	28 (32.6)	1.679 (1.326-2.124)	0.000

*p-value significant; **crude oods ratio

discrimination, parental work, religion, beliefs, and abusive words. Furthermore, more than 60% of students also get discrimination from the surrounding environment, ridicule, and get physical violence. Not only that, more than 50% of respondents have been bullied in terms of finances, race or ethnicity, skin color, and physically abused.

In Table 3 based on the results of the chi-square statistical test showed that this study found that there was a relationship between Often getting body shamed bullied, Often getting physically bullied, Often getting discriminated against intelligence bullied, Often getting bullied in terms of parental profession, Often getting bullied in terms of religion and belief, and Often get bullied in terms of harsh words with significance values ($p<0.05$) and risks ranging from 2.05 times to 3.71 times.

Discussion

Based on the results of the study, the sex variable showed that 53.3% of respondents were women. Furthermore, the age category gets 75.2%. According to job variables, 65.7% of respondents worked as students. At the education level, respondents showed a figure of 55.2% in high school. Next the variable length of sleep time there is a figure of 51.4% in the category of >at 10 pm. The results of this study in line with Novilia & Budiman showed that the frequency distribution in characteristics is based on the sex of respondents with the majority in men as many as 79 respondents (43.6%) and women as many as 102 respondents (52.4%).[11] This study also contradicts Nauli *et al.*[12] that generally the respondents are between the age of 10 years, which is as many as 99 people (41.9%), and respondents who are between the age of 9 years as many as 86 people (36.4%).This is also different from Devita & Dyna who showed that Bullying behavior is 0.6 times more likely to happen to a mother. And results also showed a 2,955 times greater risk of bullying behavior in children.[13] Research conducted by Lestari *et al.*[14] showed that 96% of students of State High School 15 Bandar Lampung committed bullying behavior. Research conducted by Prihatiningsih & Wijayanti, there is a meaningful relationship between sleep disorders and emotional and mental disorders. This is based on the Chi-Square test result of 0.044 (<α 0.05).[15]

Based on the results of studies on the category of factors of bullying behavior on student mental health reported that more than 70% of students were bullied by body shaming, parental work, in terms of religion and beliefs, etc., and above 60% received discrimination from the surrounding environment, physical violence, and others, and more than half of respondents were bullied financially, ethnic race and skin color and harassment. In another study conducted by Aminah *et al*.[16] Students who do forms of physical bullying behavior are several 121 students or 44% and students who do not have Physical bullying behavior amounted to 156 students or 56% of the overall sample. The results of the study conducted by Geofani, 2019 stated that it was obtained Thitung 6,963 is greater than Ttabel, which is 1,984, with a significance level of 0.000 smaller than α=0.05, so it can be concluded that Variable X affects variable Y, it can be concluded that there is The influence of cyber bullying body shaming on Instagram social media on the confidence of career women in Pekanbaru.[17]

The results of the statistical test also found a relationship between frequent physical bullying, body shaming, discrimination of intelligence and the surrounding environment, parental work, religion, and abusive words, namely ($p<0.05$), and having a risk range ranging from 2.05 to 3.71 times. Based on previous research conducted by Kumbara *et al.*[18] in line with this study, student anxiety of 58.75% or 94 answers stated yes anxiety is derived from the aspect of somatic anxiety and 41.25 or as many as 66 answers expressed no anxiety sourced from the somatic anxiety aspect.According to Harahap and Ika Saputri, the subject feels uncomfortable then feels inferior and feels unappreciated so the subject limits themselves in socializing. The statement can be seen in the interview results, "Traumatic, sis, so do not want to be close to him and do not want to bales treatment he, sis" it is contrary to this study.[19] Research by Sari & Hidayati showed that there is a significant negative relationship between self-concept and loneliness. Hypotheses that suggest a negative relationship between self-concept and loneliness are accepted. The coefficient of determination (R square) of 0.585 means that self-concept contributes an effective 58.5% to loneliness in adolescents.[20] Based on research Lalenoh *et al* state that it is known that most students have a minimal risk of suicidal ideation (77.2%), but some students have a risk of a suicidal idea that is low to high risk.[21]

This study is in line with Chintya *et al*. Participants with criteria for non-working

work under the age of 19 vented sadness by shouting, being alone, hitting friends, and injuring or hurting themselves (for example, by hitting a glass/ mirror). While participants with a background in housewife work chose to squeeze sago, blame themselves, destroy items in the form of plates, and go to the garden and escape. In addition, participants said that it takes time to relieve sadness, which can be in a matter of a few days. Here are the participants' expressions: "Choosing to shout" (P1:220-225) "Yes alone, self-harm" (P2:85-95) "this must go to the hamlet, must go to the garden" (P3:215-220)" "Choosing to be silent." (P4: 105-110) "It can be sad." (P2:50-55) "Throw the plate." (P2:65-70) "Injuring, usually mashing glass, chose to escape because he ran to calm down." (P2: 70- 75) "Maybe one week like that." (P4: 110-115) "Have to leave this house to go to the garden." (P3: 215- 220) "Venting profanity." (P3 105-110) "Angry" (P8: 5ss5-58) "Destroy the plate so" (P4 95-10)[22]. Research conducted by Hidayati that of 254 study subjects, there were 73 subjects, or 28.7% had high self-compassion, and 181 subjects or 71.3% had low self-compassion. There were 134 subjects or 52.8% who had high loneliness and 120 subjects or 47.2% who had low loneliness.[23]

Based on the results of the research outlined above, there are several conclusions, namely as follows: The results of the study found that as many as 10–60% of school students in Indonesia, at least once a week get unpleasant treatment from bullies either in the form of non-physical such as scorn, ridicule, exclusion, or in the form of physical bullying treatment such as beatings or encouragement. In the characteristic distribution of subjects' length of sleep, 51.4% of respondents had >10 p.m. sleep hours. The distribution of bullying behavior is on variables ever physically bullied there 3.8% of respondents answered often. Furthermore, getting bullied body shaming by 11.4% in the category often. Based on the mental health distribution there is 7.6% on variables of feeling anxious and thinking hard in the category often. Furthermore, for the category of feeling scared, 5.7% of respondents answered often. Based on variables feeling useless there were 10.5% of respondents in the frequent category. Furthermore, the category of ever thinking about suicide shows a figure of 2.9%. After that, variables once cried so much, pulling hair, and blaming yourself showed 3.8% in the category often. While variables feel alone and no one cares about the category there is often a figure of 13.3%.

Based on the conclusions above, there are suggestions in this study: For the perpetrator: never bully someone, because a little bad action and speech from you both verbally and physically will have a very big impact on the person. For victims: never want to be bullied, reduce your bad taste, and dare to say no because everyone has the right to it, if you get action immediately report it to teachers, lecturers, or officers in schools and campuses. For parents: pay more attention to the child, because the bully does this is the cause is the lack of attention from his parents and he envies seeing his friend who gets more attention from his parents. For Health Workers: Provide counseling that is more related to mental health and bullying behavior and its impact on the school environment, campus, etc. For Counseling Guidance Teachers: Be a place to vent for students who are in school or on campus, when they vent do not be scolded, but try to be like friends and understand the student and do not be told secrets from the student to others.

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Diabetes Retinopathy Prevalence and Risk Factors among Diabetic Patients Seen at Highland Eye Clinic Mutare Zimbabwe: A Retrospective Study

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Abstract

Objective: To determine the prevalence of diabetic retinopathy and its association with hypertension, age, gender, and fasting blood glucose level.

Methods: This retrospective study assessed the prevalence of diabetic retinopathy with its associated risk factors on 135 diabetic patients, aged 18 years and above, visiting the Highland Eye Clinic Mutare, Zimbabwe. Data were collected on the age, sex, and type of retinopathy. Based on the identified retinopathy, subjects were divided into no retinopathy, non-proliferative diabetic renopathy, and proliferative diabetic retinopathy groups. Analysis were then performed using multivariate and univariate regression analyses to test the association between the presence of retinopathy and several risk factors, and results were presented in percentages, with $p<0.05$ considered to show statistical significance.

Results: The average age of the subjects this study was 60.8±14 with female subjects constituted more than half of the total number of subjects (58.5%). Forty four percent were overweight (BMI 25–30), 34.8% were obese, and the overall prevalence of diabetic retinopathy was 31.1% (non-proliferative diabetic renopathy, 20%; proliferative renopathy, 11.1%). The proportion of subjects with retinopathy increased with duration of DM, being 23.3% in those with a DM duration of less than 10 years and 46.6% in those with a DM duration of more than 10 years. Age and hypertension were significantly associated with the presence of diabetic retinopathy ($p<0.05$) in univariate analysis, but no association was identified between retinopathy and fasting blood glucose (chi-square test, $p=0.0965$)

Conclusion: The prevalence of diabetic retinopathy (DR) is high (31.1%), Non-proliferative DR is more common than the proliferative (DR). There is a strong association between diabetic retinopathy, hypertension, and age.

Keywords: Diabetes, hypertension, prevalence, retinopathy

Introduction

Diabetes mellitus is a chronic heterogeneous metabolic disorder with complex path oogenesis. It is the main characteristics is hyperglycemia, due to abnormalities in either insulin secretion or insulin action or both. Long-term Diabetes mellitus leads to various microvascular and macrovascular diabetic complications, including retinopathy which is mainly responsible for diabetes-associated morbidity and mortality[1]. The most prominent risk of diabetes mellitus is diabetic retinopathy, which is recognized as a disorder for the smallest blood vessels in the eye. It's soon becoming a global

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public health issue. [2-4]Diabetic retinopathy is one of the most common microvascular complications of diabetes and irreversible blindness-causing disease in the population. In particular, proliferative retinopathy is a unique complication of diabetes and is rarely associated with other diseases.[4] In 2020, the number of adults worldwide with Diabetic retinopathy (DR), vision-threatening diabetic Retinopathy (VTDR), and clinically significant macular edema (CSME) was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively; by 2045, the numbers are projected to increase to 160.50 million, 44.82 million, and 28.61 million, respectively. This report highlighted DR as a potential challenge worldwide. Diabetic retinopathy prevalence was highest in Africa (35.90%) and North American and the Caribbean (33.30%) and was lowest in South and Central America (13.37 %) [5]. Diabetic retinopathy is known to have a long latent asymptomatic phase during which patients do not report any signs and symptoms. As a result, patients in the later stages may experience floaters, hazy vision, distortion, and gradual visual acuity loss. Therefore, early detection of its ophthalmic complication achieved through developing tools that can be incorporated into diabetes mellitus management could be of valuable contribution in preventing ophthalmic complications which opens an avenue for this study. According to Vision Loss, Expert Group of Collaborators reported that diabetic retinopathy accounted for 0·86 million cases of blindness in those aged 50 years and older in 2020.[6] Previous studies in Saudi Arabia identified risk factors of DR including age, the duration of diabetes, glycemic control; obesity, dyslipidemia, and nephropathy.[7,8] In Saudi Arabia, nephropathy, neuropathy, insulin use, poor glycemic control, hypertension, and male gender were found to be associated with a significant increase in the risk for DR, whereas obesity was associated with a significant reduction in the risk for DR among Saudi type 2 diabetics[7]. Only a few studies evaluated the prevalence of DR in Zimbabwe leaving a gap in risk factors[9]. Currently, in Mutare Zimbabwe, the Prevalence of DR and its association with various risk factors have not yet been described despite an increasing number of diabetic patients admitted to the hospital for ophthalmic complications among other comorbidities including hypertension. Therefore the present study aimed to determine the prevalence of diabetic retinopathy, the degree to which it affects the retina and macula, and its potential association with risk factors including hypertension, BMI, age, duration of diabetes, and fasting blood glucose level.

Methods

The present study is retrospective where a total of 135 diabetic patients both male and female aged 18 and above attending Highland eye clinic located at 123 Herbert Chitepo Street Mutare Zimbabwe are enrolled in the study from the period of early November 2021 to December 2021. By means of having informed consent from the Highlands Eye Clinic to access the patient registry. The base characteristics being looked for in the 135 patients enrolled in this study are age, sex, diabetes mellitus, type of diabetes; duration of diabetes, BMI, and blood pressure. Diabetes individuals visiting the outpatient diabetic clinic, and patients over the age of 18 were used as the inclusion criteria. As for the exclusion criteria people with an exterior eye disease that obstructs retinal vision. Patients who attend the diabetic clinic regularly and meet the inclusion criteria were involved in the participation. The inclusion criteria used were: no apparent diabetic retinopathy which means no abnormalities found, non-proliferative diabetic retinopathy where micro aneurysms, dot & blot hemorrhages are found and proliferative diabetes retinopathy where one or more of the following: definite neo vascularization preretinal or vitreous hemorrhage found.

Demographic data were recorded and medical data was extracted from the outpatient booklet. The following sample size formula is used to compute the sample size: n=(Z^2 x P (1 – P))/e^2 , where Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% Confidence Interval) P is expected true proportion e is desired precision [10] Null hypothesis: we hypothesize a retrospective study of consented diabetic patients records at the Highlands Eye clinic the prevalence of diabetes retinopathy was ≤18.6% and the presence of retinopathy not significantly associated with diabetes duration, Body Mass Index and Hypertension Alternative hypothesis: A retrospective study of consented diabetic records of participants attending the Highlands Eye clinic the prevalence of diabetes retinopathy was ≥18.6% and the presence of retinopathy significantly associated with diabetes duration, Body Mass Index and Hypertension. (18.6% was the

prevalence of diabetic retinopathy found in a similar study by Tesfaye S, in Tanzania)[11]

The population of study is grouped into 3 groups No diabetics retinopathy, proliferative diabetic retinopathy, and non-proliferative diabetic retinopathy. Data collected was recorded onto an excel sheet. Each participant was allocated an identity number and his or her true identity is concealed. Excel was used to electronically manage the data.

All data were analyzed using SPSS. Data are present in percentages in descriptive patterns to characterize the prevalence. The dependent variable, the existence of diabetic retinopathy, and related independent variables were assessed using Logistic Regression analysis in addition statistical significance in terms of association was measured by Chi-square test. Variables with p-values less than 0.05 are considered significant, but those with p-values more than 0.05 are not. The odds ratio based on their confidence interval of the risk factors was explained using intervals that were created. The Africa University Health Research Ethics Committee, College of Health Sciences, and Highlands Eye clinic approved this study. Patient numbers were made used instead of their real names for the security of the patient's identities. One hundred percent confidentiality was done by me during this research. The research has been conducted under the approval of the ethical committee Africa University and all participants provided informed consent, reference of the relevant review board(s) and approval code(s) are here below. Ref: AU2266/21

Results

This study aimed to determine the prevalence of diabetes retinopathy and determination of its risk factors. The socio-demographic and clinical information of the study population indicated in term of prevalence the majority of participants are female being the most affected The average age for both men and females were 60.8±14 with no significant age difference between the two groups (male mean age was 60.2 and female mean age was 61.2). Hypertension was a common comorbidity, affecting more than two-thirds of the patients. (Table1) Only about a third of the people in the study had diabetes for more than 10 years.

The majority of the population their BMI indicated that they are overweight (44.4%), followed by (34.8%) who were obese, and (20.7%) who had a BMI that was within the recommended range. The overall prevalence of diabetic retinopathy amongst the study population was 31.1% (n=42), with 15

Table 1 Socio-demographic and Clinical Characteristics of the Study Population (n=135)

Characteristic	Frequency n (%)
Male	56 (41.5%)
Female	79 (58.5%)
Hypertensive	97 (71.9%)
AGE (Mean±SD)	60.8±14
DM duration <10 years	90 (66.6%)
DM Duration >10 years	44 (33.3%)
BMI Normal	28 (20.7%)
BMI Overweight	60 (44.4%)
BMI Obese	47 (34.8%)

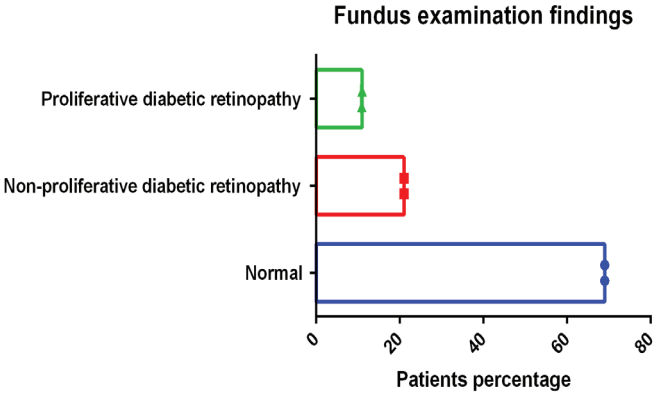

Fig. 1 Prevalence of Diabetes Retinopathy by Fundus Examination

Table 2 Proportional Relationship between Diabetic Retinopathy and Duration of Diabetes Mellitus

Duration (Years)	Number	Retinopathy Present	Retinopathy Absent	Prevalence Of Diabetic Retinopathy (%) (N_1=90, N_2=45)
0–10	90	21	69	23.3%
>10	45	21	24	46.6%

Table 3 Prevalence of Hypertension in Diabetic Retinopathy Patients (n=135)

Hypertension	Retinopathy Present n (%)	Retinopathy Absent n (%)
Yes (n=97)	30 (22.2%)	67 (49.6%)
No (n=38)	12 (8.9%)	26 (19.3%)
<40 years hypertensive	2 (1.5%)	1 (0.7%)
<40 years not hypertensive	0 (0%)	6 (4.4%)
40–59 years hypertensive	10 (7.4%)	22 (16.3%)
40–59 years not hypertensive	9 (6.7%)	16 (11.9%)
60–80 years hypertensive	13 (9.6%)	39 (28.9%)
60–80 years not hypertensive	2 (1.5%)	3 (2, 2%)
>80 years hypertensive	5 (3.7%)	5 (3.7%)
>80 years not hypertensive	1 (0.7%)	(0.7%)

participants (11.1%) discovered to have proliferative diabetic retinopathy and required urgent ophthalmologic referral, and 27 (20 %) had non-proliferative diabetic retinopathy.

Furthermore, there was an association between diabetic retinopathy and the duration of diabetes. Less than a third of the participants, 45 (33.3%) had had diabetes for a period longer than ten years while two-thirds 90 (66.7%) had diabetes for ten years or less (Table 2). The majority of the study participants were in the sixth decade of life with a mean age of 60.8±14 years (Fig. 2). The development of diabetic retinopathy was significantly associated with age (p=0.048) in univariate analysis as observed in this study in addition the prevalence was just 1.5% in the young group of under the forties, 14.1% in the 40–59 year age group and 11.1% in the above '60s (Table 5).

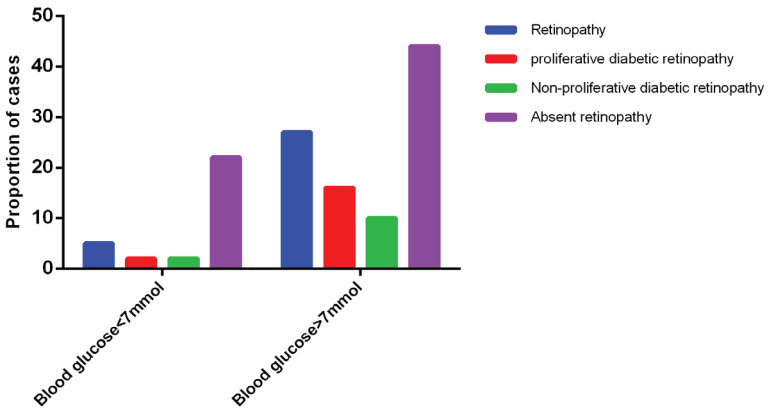

Fig. 2 Association of Diabetes Retinopathy with Fasting Blood Glucose (Chi-square test; p=0.0965)

Table 4 Diabetic Retinopathy and Fasting Blood Glucose Level (n=119)

Fasting Blood Glucose level (mmol/L)	n=119	Retinopathy Present n (%)	Non-proliferative diabetes retinopathy (n %)	Proliferative retinopathy (n %)	Retinopathy Absent n (%)
<7 mmol/L	33(27.7%)	6(5.04%)	3(2.52%)	3(2.52%)	27(22.69%)
> 7mmol/L	86(72.26%)	33(27.7%)	20(16.8%)	13(10.92%)	53(44.53%)

The majority of the study participants over two-thirds had co-existing hypertension (Table 3). There was an increase in the prevalence of Diabetic retinopathy in a Hypertensive setting (Table 3).

Furthermore, we determine the association between diabetic retinopathy and fasting blood glucose level (Table 4). However, due to some missing data, our analysis is based on 119 instead of 135. A fasting blood sugar level of less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, is indicative of diabetes.[12]

In this study 33 patients out of 119 had a fasting glucose level of 0–7 mmol/L, 6 (5%) had retinopathy of which 3 (2.5%) was non-proliferative retinopathy and the other 3 (2.5%) was proliferative retinopathy. 86 (72.26%) have a fasting blood glucose above 7 mmol/L out of 119 participants, 33 (27.7%), 20 (16.8%), 13 (10.92%) have retinopathy, proliferative, and non-proliferative retinopathy respectively are found also to have a fasting blood glucose above 7 mmol/L (Table 4). Furthermore, retrospective analysis of their proportion using Chi-square test, (p=0,0965) indicated there was no statistical significance in terms of fasting blood glucose level therefore fasting blood glucose is not associated with the development of retinopathy (Fig. 2).

We further determine diabetes retinopathy risk factors. Univariate logistic regression analysis was done on the study participants assessing the association of having diabetes retinopathy and various baseline characteristics, which are associated with the development of diabetes retinopathy as covariates (Table 5).

Discussion

According to the World Health Organization (WHO), it is estimated that DR accounts for 4.8% of the number of cases of blindness (37 million) worldwide.[13] The prevalence of diabetic retinopathy (Fig. 1) was found to be 31.1 percent (42 cases) at Highlands Eye Clinic in Mutare, with 11.1 percent (15 cases) having

Table 5 Univariate and Multivariate Analysis of Risk Factors For Retinopathy

Factor	Retinopathy		Univariate Analysis		Multivariate Analysis	
	Yes	No	Or (95% Ci)	p-value	Or (95% CI)	p-value
Gender						
Male	21	35	1.65 (0.80–3.38)	0.175	1.59 (0.49–5.12)	0.436
Female	21	58	1		1	
Age, Mean (SD)	61.5±13.2	60.4±13.9	1.02 (1.00–1.04)	0.048	1.01 (0.97–1.06)	0.615
Hypertension						
Yes	30	67	2.80 (1.23–6.42)	0.015	1.92 (0.50–7.37)	0.002
No	12	26	1		1	

proliferative diabetic retinopathy and 20 percent (27) having non-proliferative diabetic retinopathy. The findings of this study are in line with the 9-55 percent prevalence rates of diabetic retinopathy reported in Africa [14]. Less than a third of the participants, (Table 2) 45 (33.33%) had diabetes for a period longer than ten years while two-thirds 90 (66.7%) had diabetes for ten years or less. The opposite finding where found in a study by Margarete Voigt et al, with 12% having a duration below (<)10 years, and 24% after 10<15 years.[15] The finding was that those with a longer duration of diabetes are the highest risk of complications apply to this study as those with a duration less than 10 years have a lower prevalence of DR (23.3%) and those with a duration greater than 10 years had a prevalence percentage of 46.6%. The disparity between the research might be a reflection of the shifting diabetes environment, which is ascribed to a global increase in the diabetes pandemic caused by sedentary lifestyles, urbanization, high-calorie diets (carbohydrates are cheaper than protein in Zimbabwe), and obesity. Additionally, the socio-economic changes in Zimbabwe have impacted negatively healthcare delivery and consequently the quality of diabetes care that is putting into account the increasing inflation taking place.

In this study, it was found males (37.5%) are more affected than females (26.6%) (Table 5). This study's finding is in agreement with the findings of a study conducted in rural southern China where a higher prevalence of diabetic retinopathy was found in men[16]. It is important though to note that the role of gender alone as a determinant of diabetic retinopathy is yet to be unraveled since the fulcrum to which gender has an effect is solely based on hormones and these differ in consideration to race, diet, and lifestyle. The majority of the study participants were in the sixth decade of life with a mean age of 60.8±14 years. The development of diabetic retinopathy was strongly associated with age as observed in another study[17] Maladaptive alterations and complicated interactions between the autonomic nervous system, a maladaptive immune system, increased activation of the renin-angiotensin-aldosterone system (RAAS), and unfavorable environmental variables are all involved in the pathogenesis of hypertension in diabetes. The majority of the study participants in excess of two-thirds had co-existing hypertension (Table 5). There was a strong association of diabetic retinopathy in the setting of hypertension with 97 of the 135 diabetic patients looked at in this study being hypertensive, Similar findings were observed in investigations which found also a strong association between diabetic retinopathy and hypertension [18] [19]. Studies have shown that the relative risk of diabetic retinopathy for diabetics also having hypertension is 1.7.[20, 21] In a Univariate logistic regression analysis, the prevalence of diabetic retinopathy was higher in those who had diabetes for more than 10 years vs. less than 10 years, and this was statistically significant (OR 1.10 (95 percent C1 1.00–1.01), p=0.011). This was similar to Basal et al, study indicating there is an increasing prevalence of DR with an increase in the duration of DM.[22] In a multivariate logistic regression study, the duration of diabetes mellitus OR 1.01 (95 percent CI 1.00–1.01) and being hypertensive OR 1.92 (95 percent 0.50–7.37) were found to be highly linked with developing diabetic retinopathy. The discovery of a substantial link between the development of diabetic retinopathy and the length of diabetes mellitus reflects the pathophysiology of diabetic retinopathy and the influence of long-term hyperglycemia exposure. This study supported previous results that the longer a person has had diabetes, the greater the chance of developing diabetic retinopathy.[22] The progression of retinopathy is accelerated by long-term hyperglycemia.[23]

Out of the 119 participants, 18 (15.1%) had uncontrolled fasting blood glucose and of these 9 (7.6%) had diabetic retinopathy. (table3, 5) A study done by Yumi Matsushita NT et.al[24] clarified that the higher the level of fasting blood glucose, the higher the prevalence of retinopathy, and there was no clear threshold, also suggesting that it is possible to detect the risk of retinopathy using fasting blood glucose only. In addition, a study indicated that decreased retinopathy risk could be achieved with tighter blood glucose control.[25] While our study revealed contradictory results when compared to the afford mentioned study since in our research setting the prevalence of diabetes retinopathy is associated with uncontrolled blood glucose levels is only about 7%. To prevent retinopathy, it is clear that fasting blood glucose levels should remain at a low level. Only about a third of the people in the study had diabetes for more than 10 years. 44.4 percent of the individuals were overweight, followed by 34.8 percent who were obese, and 20.7 percent who had a BMI that was within the recommended range. Although there is no solid evidence that obesity causes DR as indicated by a recent study where neither

being overweight nor obese is associated with an increased risk of DR.[26] However another report indicated that increased body mass index is associated with an increased risk of diabetic retinopathy.[27] Obesity (BMI>31.0 kg/m2 for males and 32.1 kg/m2 for women) was linked to retinopathy development and severity in T2DM patients where higher BMI is associated with retinopathy.[13] Documented records of those patients' medical history at high land eye clinic indicated they have mainly type II diabetes mellitus.

This study was able to evaluate the prevalence of diabetic retinopathy among the 135 participating diabetic patients attending Highlands Eye Clinic in Mutare, Zimbabwe as 31.1%. In addition, Non-proliferative diabetic retinopathy is more common than proliferative retinopathy. Age, Hypertension, are significantly associated with diabetic retinopathy. The present study has some limitations as follows: our population is limited, the study was only conducted on a few participants that were available in the Highland Eye clinic, and in addition due to limited resources this study was only in Mutare, in Manicaland province, therefore, we cannot generalize our findings to the country of Zimbabwe.

In conclusion, the overall prevalence of diabetes retinopathy was found to be 31.1% Non-proliferative diabetes retinopathy is more common than proliferative diabetes retinopathy. There was a strong association between diabetic retinopathy, hypertension, and age. The present report uncovers risk factors associated with the development of retinopathy which if properly taken into account will attenuate visual damage caused by diabetic retinopathy during the asymptomatic period.

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Validity and Reliability of The Indonesian Version of Patient Allergic Rhinitis Questionnaire and Allergic Rhinitis Prevalence in A Class of 2018–2019 Medical Students of Universitas Padjadjaran, Indonesia

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Abstract

Objective: To determine the validity and reliability of the Indonesian version of Patient Allergic Rhinitis Questionnaire as a screening tool for AR and the prevalence of AR in a class of 2018–2019 medical students of Universitas Padjadjaran, Indonesia.

Methods: A cross-sectional descriptive study was performed during the period November-December 2021 on a class of 2018–2019 medical students of Padjadjaran University. The Indonesian version of the pre-validated Patient Allergic Rhinitis Questionnaire was distributed online. Allergic rhinitis was determined from history taking by identifying a history of a previous diagnosis of AR and/or 2 or more symptoms (watery runny nose, sneezing, nasal congestion, itching, or conjunctivitis) for more than 1 hour on most days.

Results:. The validity of the Indonesian version of the Patient Allergic Rhinitis Questionnaire was good with a 0.895 Cronbach's Alpha coefficient, reflecting a reliable questionnaire. The prevalence of AR was 35.8% with most were female (69.2%). There were 59.9% of respondents who had a history of allergy in their parents. The most common symptom was nasal congestion (85.7%) and the moderate-severe persistent (49.2%) was the most common ARIA-WHO classification. Dusty places (92.1%) were the most common cause of symptoms. The most common comorbidity was rhinosinusitis (35%). The mean symptom severity score was 6.7.

Conclusions: The Indonesian version of the Patient Allergic Rhinitis Questionnaire is valid and reliable as a screening tool for AR. The prevalence of AR in this study is quite high, with moderate-severe persistent as the most prominent classification.

Keywords: Allergic rhinitis, patient allergic rhinitis questionnaire, prevalence, reliability, validity

Introduction

Allergic rhinitis (AR) is a disease of the nasal mucosa mediated by immunoglobulin E (IgE) after exposure to allergens. The classic symptoms of AR include an itchy nose, sneezing, rhinorrhea, and nasal congestion. In addition, AR can also cause allergic rhinoconjunctivitis symptoms which are characterized by the presence of watery, red itchy eyes.[1,2] Allergic rhinitis comorbidities include asthma, rhinosinusitis, nasal polyps, otitis media with effusion, adenoid hypertrophy, and gastroesophageal reflux.[1,3,4]

According to the World Allergy Organization (WAO), it is estimated that forty percent of children and about ten to thirty percent of adults are affected by AR worldwide.[3] In the Asia-Pacific region, the prevalence of AR is ranging between 4.5–

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80.3%.[5] Meanwhile, the prevalence of AR in Indonesia is not known for certain because there is no national data on this matter, but there was a study on a class of 2010 medical students of Padjadjaran University which showed that the prevalence of AR was 38.2%.[6]

Allergic rhinitis can decrease quality of life by impairing cognitive function and sleep and also causing fatigue and irritability. Allergic rhinitis is also associated with decreased productivity at work and school.[1] In addition, AR can have a direct economic impact due to the cost of medicines and consultations and an indirect impact due to decreased work productivity.[3]

The diagnosis of AR is made based on the history taking, physical examination, and supporting examination such as skin prick test or allergen-specific IgE test which is then classified based on the duration of symptoms and the severity of symptoms by referring to the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendation guideline in collaboration with the World Health Organization (WHO).[1] Skin prick test is the gold standard diagnostic tool for AR. The advantages of the skin prick test are that the examination is fast, simple, and well-tolerated by patients.[1,7] Meanwhile the disadvantages are that special training is required for health workers and this examination reagent is not always available in health services in Indonesia.[7] The use of a validated questionnaire is an alternative tool to screen for AR in first-level health services which according to the ARIA-WHO recommendation is the use of the Patient Allergic Rhinitis Questionnaire.[8] However, in Indonesia there has been no study using this questionnaire yet.

Medical students are a productive age group who need a fast and accurate diagnosis of AR because of their need for a good quality of life. Meanwhile, during a pandemic, there is limited interaction between patients and doctors, which affects the initial screening for AR. This study aims to determine the validity and reliability of the Indonesian version of the Patient Allergic Rhinitis Questionnaire as a screening tool for AR when it is not possible to meet the patient in person or the skin prick test reagent is not available and to determine the prevalence of AR in a class of 2018-2019 medical students of Padjadjaran University.

Methods

This is a descriptive study with a cross-sectional design. Approval was received from the Research Ethics Committee of the Faculty of Medicine of Padjadjaran University, Indonesia with ethics letter number 850/UN6.KEP/EC/2021. The type of data used is primary data through online questionnaires obtained from November to December 2021.

The research subjects were the class of 2018–2019 medical students of Padjadjaran University with inclusion criteria aged 17–23 years, exclusion criteria were subjects who were not willing to fill out the questionnaire or had become respondents to the validity and reliability test of the questionnaire. The sampling technique used a cross-sectional formula for categorical descriptive so that the sample size in this study is a minimum of 363. The total number of class 2018-2019 medical students at Padjadjaran University is 669 students. Thirty students took the validity and reliability test of the questionnaire and there were difficulties in contacting some students such as the unavailability of contacts and no response from some students so there were only 390 students involved in this study.

The research instrument is an online questionnaire consisting of an explanation of the research and research objectives, research ethical approval, informed consent, respondent's identity and AR history, Patient Allergic Rhinitis Questionnaire, and 1 additional question. The Patient Allergic Rhinitis Questionnaire section has been translated into Indonesian and has been validated first. This questionnaire consists of 5 questions regarding AR consisting of 1 question regarding AR symptoms, 1 question regarding the causes of AR symptoms, 1 question regarding the duration of AR symptoms, and 1 question regarding the impact of AR symptoms. All questions can be answered with a choice of "yes" or "no" except for the question of how bothersome the symptoms of AR are which is answered with a choice of numbers from 0 (not bothersome at all) to 10 (very bothersome). Meanwhile, in the additional question section, there is a question regarding the presence of at least 2 AR symptoms that occur for more than 1 hour on most days with the answer choices being "yes" or "no".

The validation of the questionnaire was carried out by translating the original version of the questionnaire from English to Indonesian at the IEDUC (International Education Center) institution which was then examined by our supervisor in Otolaryngology-Head and Neck Surgery field. The translated questionnaire

was distributed to 30 class of 2018 medical students of Padjadjaran University which was then tested for validity using the Corrected Item-Total Correlation method and tested for reliability using Cronbach's Alpha method.

Results

In assessing the validity of the Indonesian version of the Patient Allergic Rhinitis Questionnaire, the point-biserial correlation is between 0.352 to 0.709 which indicates that this questionnaire is valid because the point-biserial correlation is more than 0.25 (Table 1).[9] Meanwhile, the Cronbach's Alpha coefficient is 0.895 which indicates that this questionnaire is reliable because a questionnaire is considered reliable if the Cronbach's Alpha coefficient is at least 0.7.[10]

After obtaining a valid and reliable questionnaire, the questionnaire was distributed to research subjects to assess the prevalence of AR. From the 390 subjects, the prevalence of AR was 140 people (35.8%) with females (69.2%) higher than males (30.7%). Meanwhile, there were more subjects with a history of allergy in their parents (59.9%) than those without a history of allergy in their parents (40%) (Table 2).

According to the cause of AR symptoms that the subjects suffered, the most common cause was dusty places (92.1%) followed by

Table 1 Validity Test Result of the Indonesian Version of Patient Allergic Rhinitis Questionnaire

Questions	Point Bi-serial Correlation	Result
1. Apakah Anda sedang mengalami gejala berikut ini atau pernah menderita gejala tersebut?		
Hidung berair	0.695	Valid
Bersin-bersin (terutama dengan keras dan terus-menerus)	0.515	Valid
Hidung tersumbat (perasaan sulit bernafas melalui hidung)	0.669	Valid
Hidung gatal	0.703	Valid
Mata merah, gatal dan berair	0.709	Valid
2. Apa yang menyebabkan gejala yang Anda derita?		
Serbuk sari dari pohon, bunga dan rerumputan	0.410	Valid
Jamur (baik di dalam maupun di luar ruangan)	0.496	Valid
Hewan berbulu (terutama kucing, anjing dan tikus)	0.352	Valid
Tempat berdebu	0.433	Valid
3. Berapa lama Anda menderita gejala tersebut?		
Lebih dari empat hari dalam seminggu	0.489	Valid
Lebih dari empat minggu berturut-turut	0.496	Valid
4. Bagaimana gejala tersebut memengaruhi Anda?		
Gejala itu mengganggu tidur Anda	0.668	Valid
Gejala itu menghambat kegiatan harian Anda (olahraga, rekreasi, dll.)	0.695	Valid
Gejala itu menghambat partisipasi Anda di sekolah atau tempat kerja	0.572	Valid
Gejala itu merepotkan Anda	0.642	Valid

Table 2 Characteristics of Respondents

Characteristics	Allergic Rhinitis (n=140)		Non-Allergic Rhinitis (n=250)	
	n	%	n	%
Sex				
Male	43	30.7	67	26.8
Female	97	69.2	183	73.2
Parental allergy history				
Mother or father	62	44.2	78	31,2
Both parents	22	15.7	14	5.6
No history	56	40	158	63.2

furred animals (31.4%) and pollen (11.4%). Mould (8.5%) was the least common cause of AR symptoms (Table 3).

Allergic rhinitis subjects were then classified based on the history of symptoms they had or were experiencing. Subjects can choose one or more symptoms. The most common symptom of AR was nasal congestion (85.7%) followed by a watery runny nose (84.2%), sneezing (83.5%), itchy nose (82.8%), and then red, itchy, and watery eyes (67.8%) (Table 3).

The most common AR comorbidity was rhinosinusitis (35%). After rhinosinusitis, the most comorbidities were asthma (21.4%) and gastroesophageal reflux (13.5%). Otitis media with effusion (4.2%), adenoid hypertrophy (2.8%), and nasal polyps (0.7%) were relatively few comorbidities (Table 3).

Table 3 Frequency of the Cause of Symptoms, Symptoms, and Allergic Rhinitis Comorbidity

	Number of respondents	
	n	%
Cause of symptoms		
Pollen from trees, flowers, and grasses	16	11.4
Mould (both indoors and outdoors)	12	8.5
Furred animals (especially cats, dogs, and mice)	44	31.4
Dusty places	129	92.1
Symptoms		
Nasal obstruction	120	85.7
Itchy nose	116	82.8
Watery runny nose	118	84.2
Sneezing	117	83.5
Watery, red itchy eyes	95	67.8
Allergic rhinitis comorbidity		
Asthma	30	21.4
Rhinosinusitis	49	35
Nasal polyps	1	0.7
Adenoid hypertrophy	4	2.8
Otitis media with effusion	6	4.2
Gastroesophageal reflux	19	13.5

Table 4 Prevalence of Allergic Rhinitis based on ARIA-WHO Classification

Classification	Number of Cases	
	n=140	%
Mild intermittent	14	10
Moderate-severe intermittent	54	38.5
Mild persistent	3	2.1
Moderate-severe persistent	69	49.2

Then the AR subjects were classified using the ARIA-WHO classification based on the duration of symptoms and the severity of the symptoms into mild intermittent, moderate-severe intermittent, mild persistent, and moderate-severe persistent. From the results of this study, it was found that the classification of AR from the highest to the lowest was moderate-severe persistent (49.2%), moderate-severe intermittent (38.5%), mild intermittent (10%), and mild persistent (2.1%) (Table 4).

On a Visual Analogue Scale (VAS) symptom score of 0-10, subjects chose the extent to which AR symptoms bothered them. Overall, there were variations in the symptom severity scores chosen by the subjects, starting from the lowest score of 0 to the highest score of 10. The mean symptom severity score was 6.7 with a standard deviation of 1.9 (Table 5).

Discussion

The prevalence of AR in this study was slightly higher than the prevalence of AR proposed by WAO, which ranged from 10–30% globally.[8] In addition, the prevalence of AR in this study was also higher than the prevalence of AR studied in Korea (17.1%) and Nigeria. (22.8%).[11,12] The difference in the prevalence of this study with other studies can be caused by the large and the age range differences of the population used. The population study conducted in Korea is a population that represents Korean citizens as a whole with a total sample of 85,006 subjects aged less than 2 years to more than 60 years.[11] Meanwhile, in a study conducted in Nigeria, the population represents 5 geo-political zones in Nigeria with a total sample of 20,063 subjects aged 6 years to more than 18 years.[12] In addition, the variations in risk factors between regions such as risk factors of environmental conditions and the presence of a family history of allergy can also be the cause of the different prevalence of AR in this study with other studies.[1] However, the prevalence of AR in this study was slightly lower than in the previous study in a class of 2010 medical students of Padjadjaran University which was 38.2%.[6]

The result of this study showed that the prevalence of AR was higher in females than in males. The research conducted by Fauzi and Ha also showed that AR in females was higher than in males.[6,11] In this study, the research subjects involved are higher in females than males so it can cause female AR subjects to be higher than males. This is also supported by the absence of differences in the early pathogenesis of AR in both females and males so females should not be more likely to have AR than males.[13] However, some studies stated that the prevalence of AR is higher in males and there are fundamental differences between females and males in the inflammatory pathway towards allergen, causing AR to occur more often in males than females.[14]

Allergic disorders involve important gene-environmental interactions.[3] One of the AR risk factors is a family history of allergy. The genetic contribution to allergic disease is estimated to be greater than 50%.[14] The inheritance of risk alleles in many genes has increased the susceptibility to allergic disease.[3] In this study, AR subjects who had a history of allergy in their parents were higher than those who did not have any history of allergy in their parents. This study also showed that the history of allergy in their mother or father was higher than those who had a history of allergy

Table 5 Central Tendency and Dispersion of Symptoms Severity Score

	Lowest score	Highest score	Mean	Deviation standard
Sex				
Male	1	10	6.6	1.9
Female	0	10	6.7	2
All Subjects	0	10	6.7	1.9

in both parents. These results are similar to a study conducted by Fauzi.[14]

The result of this study showed that the highest cause of AR symptoms was dusty places with house dust mite allergen present in it. The most common dust mite species in tropical areas such as Indonesia are *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae*. These species are abundant in mattresses, bedding, pillows, carpets, upholstered furniture, or furry toys and grow optimally in hot conditions with temperatures above 20°C and high humidity.[1] In a study conducted by Sudiro, dust mites were also the highest allergen.[15]

The ARIA-WHO classification is the current classification of AR used. The classification was made by WHO because the conventional classification that divides AR based on the time of allergen exposure into chronic, seasonal, and occupational AR is not suitable for the patient's clinical symptom status. Currently, the ARIA-WHO classification divides AR based on the duration of symptoms into intermittent or persistent and based on the severity of symptoms into mild or moderate-severe.[1] In this study, the highest classification was moderate-severe persistent. The result of this study is similar to research conducted by Basyir and Sudiro at Dr. Hasan Sadikin General Hospital Bandung which stated that the most frequent classification was moderate-severe persistent.[15,16] Most of the patients who present to the physician have had moderate-severe AR disease for more than 4 days per week and more than 4 weeks. [17]

The existence of geographical variations around the world can cause a difference in the distribution of aeroallergens, such as dust mites, in different regions. Due to environmental factors such as temperature and humidity, dust mite allergen levels vary across regions.[15] The location of this study is Indonesia, which is an area with hot and humid temperatures. This can lead to dust mites as the highest cause of allergy in this study. The high intensity and frequency of exposure to dust mites can cause many AR subjects in this study to experience AR with moderate-severe persistent classification.

Nasal congestion was the most common symptom in this study, followed by a watery runny nose, sneezing, an itchy nose, and then red, itchy, and watery eyes. Research conducted by Fauzi and Basyir stated that nasal congestion was also the most common symptom experienced by AR subjects with a percentage of 90% and 83.1%.[6,16] However, in Fauzi's study, in addition to nasal congestion, an itchy nose was also the most frequent symptom (90%).[6] Nasal congestion can occur due to the presence of mediators such as histamine and leukotriene which increase vascular permeability and then edema formation.[17] Nasal congestion is the most disturbing symptom in AR patients and can interfere with the patient's quality of life such as decreased work productivity.[1] One of the main symptoms found in AR with moderate-severe classification is nasal congestion.[18] This corresponds with the result of this study that showed the highest AR symptom and the highest ARIA-WHO classification based on the symptom severity are nasal congestion and moderate-severe consecutively.

In this study, the most common AR comorbidity was rhinosinusitis. This can occur due to an allergic reaction in the nasal mucosa that can cause swelling so can obstruct the ostium of the sinuses and there is more inflammation in the maxillary sinus of allergic patients.[19] The result of this study is higher than the study conducted by Moeis at Dr. Hasan Sadikin General Hospital Bandung which stated that patients with rhinosinusitis comorbidity were only 9.6%.[20]

According to ARIA-WHO, more than 80% of asthmatic patients have rhinitis and 10–40% of rhinitis patients have asthma. This represents the concept of one airway one disease.[1] Because of their pathophysiology and histology similarity, AR and Asthma are considered to be similar allergic airway diseases in different locations.[4] In this study, asthma comorbidity was the highest comorbidity after rhinosinusitis. This result is slightly lower than the result of research conducted by Moeis which stated that asthma comorbidity was 24.6%.[20]

The highest comorbidity in this study after rhinosinusitis and asthma was gastroesophageal reflux disease (GERD). Feng's research showed that AR patients are at greater risk for developing GERD than non-AR patients. Due to itching in the throat and nasal discharge that drips into the posterior nose, there is an increase in the frequency of swallowing in AR patients. This high frequency of swallowing can exacerbate gastric acid backflow by increasing transient lower esophageal sphincter relaxation (TLESR). In addition, the presence of eosinophilic inflammation in AR may exacerbate the inflammatory response in GERD. This is because the allergic impact of AR on the nasal mucosa can have the same impact on the

laryngeal mucosa such as edema and excess mucus secretion, causing the symptom of laryngopharyngeal reflux which is a subgroup of GERD.[4]

Allergic rhinitis can decrease quality of life and productivity.[1] In this study, the standard deviation is smaller than the mean, which indicates that the data distribution is mostly close to the mean so the mean score is a good representation of the overall data. This study shows that AR has quite an impact on the quality of life of the subject.

In conclusion, the Indonesian version of the Patient Allergic Rhinitis Questionnaire is a valid and reliable questionnaire so it can be used as a screening tool for AR. The use of a validated questionnaire is very important to screen for AR if it is not possible to meet the patient in person or the skin prick test reagent is not available. This questionnaire can be easily used by health workers to screen for AR. However, the questionnaire should be added with 1 additional question regarding the presence or absence of at least 2 AR symptoms that occur for more than 1 hour on most days to be able to determine whether the patient has AR or not according to the ARIA-WHO guideline. The study shows a quite high prevalence of AR with the highest classification being moderate-severe persistent, which means there is an importance to holding socialization about AR so that AR patients can detect and treat AR early to have a good quality of life. In addition, it is advisable to conduct research both online and offline and also provide incentives for subjects who are willing to participate so it will yield a greater quantity of involved research subjects and then can produce more accurate data.

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Knowledge and Practice of Menstrual Hygiene and Reproductive Tract Infection in Adolescent Girls in Doda District of Jammu and Kashmir Territories, India

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Abstract

Objective: To assess knowledge and practices regarding menstrual hygiene and reproductive tract infection in adolescent girls in Doda District of Jammu and Kashmir Territories, India.

Method: This cross-sectional study was performed on adolescent girls attending schools in Doda district of Jammu and Kashmir territories, India. Data were collected through interviews using a predesigned semi-structured questionnaire and results were analyzed using MS Excel.

Results: A total of 450 adolescent girls from public and private schools of Doda district of Jammu and Kashmir were included in this study. Most participants were in the 14–16 years of age. The most common source of information about menstruation identified in this study was mother (56.2%), sister (13.1%), teacher (12.7%), and friends (9.6%). In terms of menstrual hygiene, 53.1% girls used sanitary pads, 24% girls used dry cloths/towel and 10.7% girls used homemade and sanitary pads during their menstrual period. About 42% of the participant were absent from school during their menses and most participants take daily bath during their menses.

Conclusion: Awareness regarding menstruation and menstrual hygiene needs to be improved with the emphasize on providing accurate and adequate information on this topic to adolescent girls. Information and provision on affordable absorbent napkins or pads during menstrual period are also important for these girls.

Keywords: Attitudes, clothing, health knowledge, menstrual hygiene, reproductive tract infection

Introduction

In females, menstruation is a universal and natural process during the reproductive age. Yet, often when a girl sees blood first time (menarche) from her vagina, can be shocking and frightening[1]. In India, the physiological bases of menstruation, biological changes at puberty, and infection risks by poor practices are hardly ever discussed openly.

Around 40–45% of adolescent girls have less knowledge and unsafe hygienic practice regarding their menstrual flow.[2] This might have a clinical implication to integrate the promotion of menstrual hygienic practice in the health care system and comprehensive efforts including policy implication are needed to improve girls' knowledge and safe hygienic practices towards menstruation right from their adolescent period.[3] In this community, menstrual hygiene remains considered a taboo subject; many females feel uncomfortable discussing it in public.[4]

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Reproductive tract infections (RTIs), both sexually transmitted infections (STIs) and non-Sexually transmitted infections (non-STIs) of the reproductive tract, are accountable for major illhealth throughout the world. The WHO estimates that every year, there are over 340 million new instances of STIs wherein 75–85% arise in growing countries. In India alone, forty million new cases emerge every year. A majority of women suffering from RTIs have complications like pelvic inflammatory disease (PID), infertility, cervical cancer, puerperal sepsis, chronic pelvic pain, and ectopic pregnancy. Among women, RTIs in lots of cases are asymptomatic, making their detection and prognosis difficult.[2] Several types of research carried out amongst adolescent and pretertiary college students internationally, have shown insufficient knowledge of menstruation and poor menstrual hygiene practices.[5, 6]

So, it becomes an important area of study to evaluate the knowledge and the menstrual hygiene practices that female comprehends and rectify by educating them. Hence the present study aimed to assess the knowledge regarding menstruation among school-age adolescents and to find out the practice related to the maintenance of menstrual hygiene among them.

Methods

This school-based cross-sectional study was carried out at Rural Health Training Centre (RHTC), Department of Community Medicine, and Government Medical College in Doda district of Jammu & Kashmir (J & K), from August 2019 to January 2020. A total of 6 schools (3 Government and 3 private) were selected nearby of the rural health center. Approval from Institution Ethical Committee (13/GMCD/C-MED/2019), Government Medical College, Doda, Jammu & Kashmir, was taken prior to the study.

After the selection of the schools, the respective principals explained the purpose and procedure of the study. A list of female students studying in 8th to ^{10th} grade was obtained from each of the 6 selected schools. A total of 75 students were selected from each school by stratified random sampling to obtain a total sample size of 450. 25 students were selected from each standard in every school thus allowing equal participation of all age groups.

Female students of 8th to 10th grade who had attained the menarche at the time of the study were included in this study. Students not willing to take part were excluded from the study.

Data were collected from the adolescent girls by two trained female field assistants in a private room on the school grounds. A semi-structured questionnaire was implemented for the students after obtaining informed written consent. The knowledge of the students on menstruation was based on 10 questions relating to menstrual physiology, female anatomy, and menstrual hygiene. Menstrual hygiene practice was assessed using 6 questions. The overall maximum scores for knowledge and menstrual practice were 10 and 6 points, respectively.

The questionnaire consisted of questions related to socio-demographic characteristics (religion, participant's education, parent's education, parent's occupation), and knowledge and practice regarding menstruation and menstrual hygiene (knowledge of menarche, absorbent used and practiced during menstruation). All the participants were divided into the age group of 12–13 years, 13–15 years, and more than 15 years of age. Questionnaires were distributed to the children for self-administration and care was taken that no consultations were made with fellow students with the help of school teachers.

The Data were collected using hard copy questionnaires and were entered in Microsoft Excel, coding of the variables was done and thereby interpretation and analysis of the collected data were done by using graph pad prism software. The results were expressed mostly in frequencies, percentages, and means. Associations between some variables were tested using Chi-square statistical tests.

Results

A total of 450 adolescent girls were included.

Table 1 Classification of the Participant Based on Age and Religion

Variables	n (%)
Ages (years)	
12–13	157 (34.9)
13–15	232 (51.6)
>15	61 (13.6)
Religion	
Hindu	180 (40)
Muslims	270 (60)

Table 2 Classification of the Participants According to Parent Education and Occupation

Education and Occupation	Father n (%)	Mother n (%)
Education		
No formal education	105 (23.3%)	123 (27.3%)
Primary school	93 (20.7%)	75 (16.7%)
Middle school	108 (24%)	86 (19.1%)
High school	90 (20%)	123 (27.3)
Graduate and above	54 (12%)	43 (9.6%)
Occupation		
Daily wager	153 (34%)	36 (8%)
Private job	135 (30%)	91 (20.2%)
Goverment job	87 (19.3%)	44 (9.8%)
Businessman	75 (16.7%)	-
Housewife	-	279 (62%)

Most of the adolescent girls were in the age group of 13–15 years and more than 50% of participants belonged to Muslim families. Most of the participant's parents were educated. In this study, the main sources of information about menstruation in more than 50% of participants were from the participant's mothers. About half of the participants of the present study did not have prior knowledge of menstruation before menarche.

The present study showed that only 53.1% of the participants were using sanitary pads during menstruation, 24% of the participants were using dry clothes, or towels during their menstruation and 10.7% of adolescent girls were used sanitary as well as homemade pads like dry clothes, sponges, etc. About half of the studied participants changed their pad or cloth twice a day and about 28.4% of participants cleaned their external genitalia by only using water. The hygienic practice of adolescent girls was about 12.2%.

Discussion

Adolescence is considered to be a particularly important period for women, during which significant hormonal and emotional changes occur, including the first onset of menstruation. Menstruation is a very normal physiological process at the female reproductive age, but it is surrounded by taboo and supernatural perceptions.

Menstruation is the cyclical shedding of the inner layer of the uterus and this process is controlled by the hormones secreted by the hypothalamopituitary axis.[7] Alterations in hormones during puberty initiate the transformation of a girl into a sexually mature woman, which is accompanied by psychological, cognitive, and physical changes.[8] Better appreciation and attitude towards menstruation are achieved when the adolescent girl knows about menstruation.[7] Many adolescent girls, particularly in rural regions, lack access to basic information about menstruation and related hygiene practices, and frequently join their menarche without preparation. Adolescent school girls' health and academic performance may suffer due to poor knowledge and practice of menstruation. For women and girls to manage their periods with confidence and dignity, and to make informed decisions about their menstrual health, accurate knowledge of menstruation and menstrual hygiene management is essential. In the present study was found that females having more knowledge of menstruation were better at practicing good menstrual hygiene. This study is in accordance with the many previous published articles.[2, 7, 9]

In this study were observed that the age of menstruating girls ranged from 12 to 20 years and most of the female were in the age group of 14–16 years of age. Nair *et al*.[2] in their study found the same results.In this study half of the studied participant's mother was the primary source of information about menstruation in adolescent girls. These findings are consistent with Damor *et al*.[10] Different from this study

Table 3 Participant's Knowledge of Menstruation

Variable	n (%)
Source of information about menstruation	
Mother	253 (56.2)
Sister	59 (13.1)
Teacher	57 (12.8)
Friends	43 (9.6)
Doctor	26 (5.8)
Television/radio	12 (2.7)
Age (years)	
<15	442 (98.2)
>15	8 (1.8)
Knowledge of menstruation before menarche	
Yes	212 (47.1)
No	238 (52.9)
Knowledge of menstruation (Normal process or not)	
Yes	276 (61.3)
No	135 (30)
Do not know	39 (8.7)
Knowledge of the cause of menstruation	
Disease	60 (13.3)
Hormones	147 (32.7)
Past sins	18 (4)
Curse	17 (3.8)
Do not know	208(46.2)
Sources of bleeding	
Stomach	5 (1.1)
Uterus	171 (38)
Urinary tract	159 (35.3)
Ovary	42 (9.33%)
Do not Know	73 (16.22%)

Table 4 Menstrual Hygiene Practices of Adolescents Girls

Variable	n (%)
Type of absorbent used during menstruation	
Sanitary Pad	239 (53.1)
Clean cloth/towel	108 (24)
Both cloth & sanitary Pad	48 (10.7)
Did not any absorbent	55 (12.2)
Cleans external genitalia	
With soap and water	322 (71.6)
Only with water	128 (28.4)
Frequency of changing pads and cloth during menstruation?	
≤2	255 (56.7)
3–4	150 (33.3)
≥5	45 (10)
Dispose of the sanitary pad	
Dustbin	316 (70.2)
Open space	122 (27.1)
Flush it	12 (2.7)
Practiced during menstruation	
Restrict sour foods	185 (41.1)
Restrict religious activities	98 (21.8)
Avoid sports activity	90 (20)
Restrict wearing washed clean clothes	6 (1.3)
No restrictions	71 (15.8)
Bath regularly	
Yes	436 (96.9)
No	14 (3.1)
Absent from school during menstruation	
Yes	189 (42%)
No	261 (58%)

Yasmin *et al.*[11] and Juyal *et al* [12] reported that friends and sisters became the participant's source of information.

In this study, about half of the participants did not know the cause of menstruation. The study showed, 38% of the participants know that bleeding takes place from the uterus. Chauhan *et al.*[9] in their study observed that menarche awareness was very low in adolescent girls and only very few girls considered the menstrual cycle as a physiological process. Only 11.9% of girls know that bleeding takes place from the uterus.In contrast to this study, Srivastava *et al.*[13] studied 537 adolescents in Madhya Pradesh, India, and observed that 73.7% of adolescent girls know that bleeding takes place from the uterus.

In this study, 46% of adolescent girls know the importance of sanitary hygiene and 71.7% know the risk for genital infection in unhygienic conditions during menstruation. 53% of girls use sanitary pads, 24% use dry cloth/towel, and 10.7% use a dry cloth as well as a sanitary pad. 56.7% of participants change their pads once a day, 33.3% change their pads at least twice a day and 10% changed their pads more than five times a day. This study showed that 12.2% of participants did not use any absorbent during their menstruation and most of these participants belong to the government school. 70.2% of participants wrapped their pads and disposed of a pad in a dustbin, 27% dispose of their pads in an open space and 2.7% of participants flushed their used pads. 71.7% of girls clean their external genitalia with soap and water daily while 28.3% of adolescent girls used only water for cleaning their external genitalia. Many different studies showed that menarche awareness ranges from 29% to 80% in different parts of the country and the highest seen in Chandigarh.[14-17] There are many different doubts about menstruation and they have been influenced by social myths and taboos about menstrual practices.[17]

The provision of safe, private, clean, sanitary, and hygienic facilities for dressing change, rinsing and drying materials, discreet handling options, and soap for hygiene Personalization is essential for good management of menstrual hygiene in schools. Lack of appropriate and adequate sanitation and hygiene facilities can lead to feelings of shame, embarrassment, and discomfort in girls, and may cause girls to miss school during menstruation. Even when girls go to school during their menstrual period, due to poor sanitation, they are often forced to leave school early to change the tampons used at home.[1] In this study, during menstruation, 41% of the participants did not take sour food in their diet, 21.7% avoid religious activity, 20% avoid sports activity, 1.3% of adolescents did not wear washed and clean clothes, and 16% adolescent girls did not have any restriction in any activity. The study showed, most of the participants (97%) take a daily bath during menstruation. In this study, during menstruation, 42% of adolescent girls were seen absent from school and the reason behind this was pain and discomfort.

The study results underscore that misconceptions, taboos, and myths still exist about menstruation. Reproductive tract infections, which have become a silent epidemic devastating women's lives, are closely related to poor menstrual hygiene. Unhealthy practices and social taboos during menstruation are issues that need to be addressed at all levels. A sustained public health awareness program on the physiological basis of menstruation and the adaption of good hygiene practices should be promoted with the selection of disposable sanitary napkins.

It is challenging to determine a cause-and-effect link between research variables because this is a cross-sectional study. Because this study used a self-administered questionnaire rather than an interview, the reliability of responses could not be confirmed. Again, as some respondents may claim to practice safe menstrual hygiene but do differently, the menstrual hygiene practice score may contain some social desirability biases.

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Correlation of Abdominal CT scan Score and Alpha-fetoprotein Levels in Hepatocellular Carcinoma

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Abstract

Objective: To assess the correlation between the Alpha-fetoprotein (AFP) level and characteristics of liver lesions listed in the abdominal computed tomography (CT) scan scores in hepatocellular carcinoma.

Methods: This was a retrospective analytic observational study with a cross-sectional design conducted at Sanglah Hospital in January 2017–January 2021. Subjects were patients diagnosed with hepatocellular carcinoma based on clinical and laboratory features. Samples were taken by consecutive sampling. The results of the abdominal CT scan were read by two radiologists with a predetermined abdominal CT scan scoring system. The AFP level data were taken at a maximum of 5 days before an abdominal CT scan was performed.

Results: A total of 64 subjects were included in this study. The mean serum AFP level was 1,000 IU/mL (range 0.54–61830 IU/mL). The mean abdominal CT scan score by examiner one was 10.093±5.59, while the examiner two provided a score of 10.281±5.45. The difference in mean CT scan scores between the two examiners was very low and insignificant (mean difference score -0.188; 95% CI -1.894–1.519). The rho Spearman value was 0.918 ($p<0.001$) between serum AFP levels and abdominal CT scan scores. In the partial correlation, the value of $r=0.678$ ($p<0.001$) was obtained after controlling for body mass index (BMI), age, and sex variables.

Conclusions: There is a strong positive correlation between serum AFP levels and abdominal CT scan scores in hepatocellular carcinoma patients. Further research is needed with a prospective design to reduce research bias.

Keywords: Abdominal computed tomography, alpha-fetoprotein, diffuse infiltrative, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) or liver cancer is the type of cancer that causes the most deaths from cancer, which is estimated at 781,631 deaths (8.2% of the total number) in 2018.[1] HCC is the fifth most common cancer in men and the ninth in women with an estimated worldwide incidence ranging from 500,000 to 1,000,000 new cases per year. HCC is the most common type of liver cancer globally, accounted around 75% of all liver cancers.[2] Incidence rate of liver cancer per 100,000 person-years in 2018 was estimated at 9.3 whereas the corresponding mortality rate was 8.5.[1]

Hepatocellular carcinoma is also a major health problem in Asia with hepatitis B virus (HBV) infection as the main cause.[3] It was

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estimated that around 350 million individuals are chronically infected with HBV, and 170 million individuals were at risk for developing cirrhosis and hepatocellular carcinoma.[4] Hepatocellular carcinoma is a malignancy with a poor prognosis because it is often diagnosed at an advanced stage and usually cannot be treated.[5]

Radiological examination is one of the methods used for the diagnosis of HCC.[6] The sensitivity of computed tomography (CT) scan for diagnosing HCC ranges from 67.5% (55–80%) and specificity reaches 92.5% (89–96%), while magnetic resonance imaging (MRI) has a sensitivity of 81% and specificity 85%. The feature of HCC in CT radiology is an encapsulated hypervascular mass in the arterial phase.[7] HCC has 3 (three) main types of growth patterns that can be seen radiologically: massive solitary, multinodular, and diffuse infiltrative.[8] HCC with a solitary pattern shows a single mass image with or without satellite nodules. Multinodular HCC shows multiple nodules involving large areas of the liver.[9]

Alpha-fetoprotein (AFP) is the most frequently used tumor marker for diagnosing hepatocellular carcinoma.[9] Elevated AFP levels are found in about 60% of HCC patients, and only about 10–20% of early-stage HCC patients have abnormal AFP levels.[10,11] The AFP cut-off value of 20 ng/mL showed good sensitivity but low specificity, while the cut-off value of 200 ng/mL showed high specificity, but lost sensitivity.[9] Thus, AFP has poor sensitivity in detecting liver tumors that are small in size and non-specific in diagnosing HCC, especially in the early stages.[12] Also, AFP alone for screening HCC is controversial because elevated AFP levels can occur in other benign liver conditions.

Given the performance, AFP alone is not sufficient for diagnosing HCC. Therefore, contemporary imaging techniques, such as CT scans, are needed for additional screening. Research shows a significant correlation in HCC patients between AFP levels and the characteristics of liver lesions, especially in growth patterns and the presence of portal vein thrombus using a CT scan.[13,14] Therefore, this study aims to assess the correlation between AFP levels and the characteristics of liver lesions through a CT scan in HCC at Sanglah Hospital.

Methods

This study is an analytic observational study with a retrospective cross-sectional design that assessed the abdominal CT scan of hepatocellular carcinoma patients and at the same time examined serum AFP. Based on the assessment of the two variables, an analysis was carried out to assess the relationship. The research location was at the Radiology Installation of Sanglah Hospital Denpasar in January 2017–January 2021 with the ethical clearance protocol number 2021.02.1.0260. The subjects of this study were patients diagnosed with hepatocellular carcinoma who met the inclusion and exclusion criteria, then taken consecutively until completed the number of samples was.

Inclusion criteria were all patients with hepatocellular carcinoma diagnosed through physical examination, liver function tests, and serum AFP levels were checked. Serum AFP was conducted before the abdomen CT scan examination. In addition, exclusion criteria were incomplete medical records, pregnancy, and history of other malignancies, chronic heart disease, or chronic kidney disease.

In this study, the type I error was set at 5%, the one-way hypothesis, so that Zα = 1.96. The type II error is set at 10%, then Zβ=1.28. This study refers to previous research, where a significant correlation of 0.40 was obtained.[13] The sample size for correlative analysis refers to the sample determination formula as follows:

$$\left[\frac{Z_\alpha + Z_\beta}{0{,}5 * \ln\left[\frac{1+r}{1-r}\right]}\right]^2 + 3$$

The minimum sample size required in this study is 64 people. The tools used in this study were patient medical records, data collection sheets (numbers, patient initials, AFP serum level data from medical records), and the Picture Archiving and Communication System (PACS) at Sanglah Hospital to view the results of abdominal CT-Scans in patients. Abdominal CT scans taken with coronal and sagittal reformat axial slices by a Philips Brilliance 64 CT Scan are taken precontrast phase, the arterial phase at 35–37 seconds after contrast injection, venous phase 80–95 seconds after injection and phase delay 120 seconds after injection. Also, with the CT scan tool, Siemens Somatom Go-Top 128 slices were taken precontrast phase, the arterial phase at 23-27 seconds after contrast injection, the venous phase at 60-75 seconds after injection, and the delay phase at 80–95 seconds after injection. Abdominal CT scan scoring of the

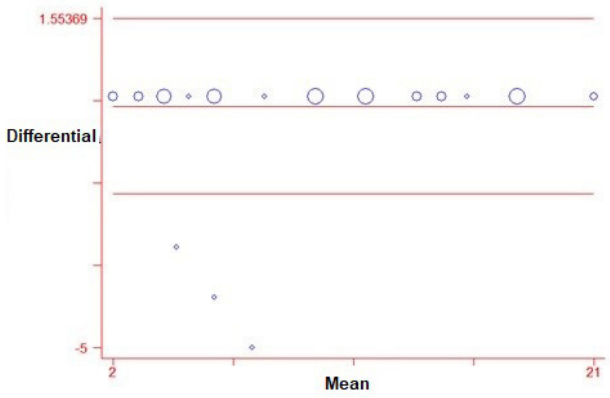

Fig. 1 Scatter Plot of the Bland-Altman Test on HCC with Abdominal CT scan

HCC was distinguished as growth type and main characteristic. HCC growth type consists of multinodular with uniform nodule size (score=1), a large massive nodule that fills one lobe of the liver (score=2), and diffuse infiltrative as small nodules (score=3). Main characteristics (score=1) were divided into arterial enhancement, disrupted capsule, thrombus tumor, irregular shape, satellite nodules, extrahepatic metastases, tumor diameter (≤2 cm = 0, >2 cm = 1), and number ≤3 pieces = 0, >3 pieces = 1). Data analysis in this study consisted of descriptive statistical analysis, Kolmogorov-Smirnov normality test, correlation test and Bland Almant limit of agreement test for the consistency test of examiner one and examiner 2, Pearson correlation test to assess the direction and strength of the correlation between AFP levels and the picture score. Abdominal CT scan in HCC, and multiple linear regression test to determine the relationship between AFP levels and abdominal CT scan scores in HCC by considering the variables of age, sex, and BMI. All of the above analysis stages use the help of IBM Statistical Package for the Social Science (SPSS) statistics 24.0.

Results

This study was conducted using medical record data at Sanglah Hospital Denpasar from January 2017–January 2021, with a total number of samples that met the inclusion criteria of 64 subjects (Table 1).

To determine the results consistency of CT scan scores, a reliability test was conducted between examiner one and examiner two using the Bland–Altman test and obtained a rho value of 0.987 (Fig.1). The result indicates a very high concordance between examiner one and two. The mean difference in CT scan scores between examiner one and examiner two was -0.188 (95% CI -1.894–1.519) (10.093±5.59 vs. 10.281±5.45), which indicates a very low and insignificant difference in mean scores between the two examiners (Fig.1).

In Fig. 1, generally, there is a very high concordance between the two examiners, i.e., most of the patients had the same score from the examinations by both examiners. Meanwhile, three samples have a fairly large difference in scores (3, 4, and 5 points). However, statistically, this difference was not significant. The correlation test for abdominal CT scan scores and AFP levels used the Spearman test because the AFP levels were not normally distributed. The Spearman test found that r=0.843, which indicates a high correlation between CT scan scores and AFP levels (Fig. 2). Furthermore, the p-value <0.001 indicates that this correlation is statistically significant.

Table 1 Basic Characteristics of Research Subjects

Characteristics	n=64
Gender	
Male, n (%)	51 (79.7)
Female, n (%)	13 (20.3)
Age (years), mean ± SB	56±11
BMI	
Underweight, n (%)	58 (90.6)
Normal, n (%)	4 (6.3)
Obese, n (%)	2 (3.1)
Serum AFP level (IU/mL), median (min-max)	1000 (0.54–61830)

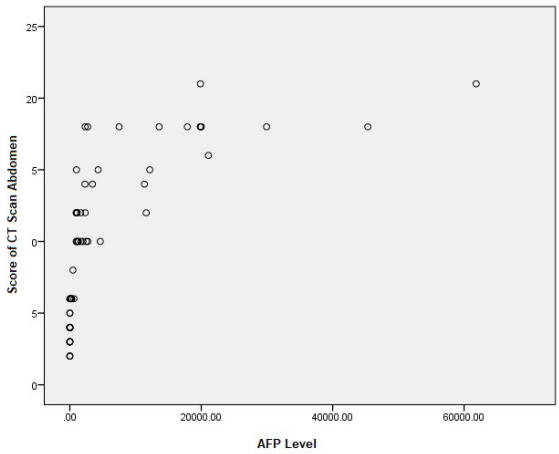

Fig. 2 Spearman Correlation Graph between AFP Levels and Abdominal CT scan Scores

A partial correlation regression test was performed to assess the relationship between abdominal CT scan scores and AFP levels by taking into account confounding variables (age, sex, and BMI) and obtained p<0.001 (r=0.460) for abdominal CT scan scores (Table 2). Meanwhile, no confounding variable was significantly correlated with increasing AFP levels (p>0.05).

Discussion

This study involved 64 subjects of patients with hepatocellular carcinoma (HCC). There were more male subjects (79.69%) in this study, almost four times more than female subjects (20.3%) (Table 1). This is by the epidemiology of HCC in general, where the incidence of HCC in men is 2–4 times the incidence in women.[2]

In most populations, the incidence of HCC is directly correlated with age up to 75 years of age. The median age at diagnosis in males is 60–64 years, while the median age in females is 65–69 years.[15] However, the median age at diagnosis is lower in Africa, i.e., 58 years in Egypt and 46 years in other African countries.[16]

Table 2 Partial Correlation between AFP Levels and Abdominal CT scan Scores in HCC

Variable	r-partial	P
AFP level	0.460*	<0.001*
Age	0.024	0.223
Gender	0.0004	0.879
BMI	0.005	0.566

*controlled for age, gender, and BMI

In this study, the mean age of the subjects was 56 years. In this study, most of the patients had a BMI classified as underweight (90.6%) compared to a normal or obese BMI. Meanwhile, according to the literature, obesity is an independent risk factor for HCC in the general population. Obesity is also a risk factor for the development of HCC from chronic viral hepatitis.[15] However, weight loss is also a common problem in cancer patients, including HCC, in 54% of cancer patients and 80% of cancer patients. patients with advanced cancer.[1] Therefore, the high number of patients with underweight BMI in this study can be explained by the weight loss commonly experienced by these cancer patients.

Hepatocellular carcinoma can produce AFP values ranging from normal to >100,000 ng/mL, approximately 30% of patients have normal AFP levels at diagnosis and can remain low, even into advanced stages. AFP >400-500 ng/mL is considered a diagnostic threshold for HCC.[15,17] In this study, median AFP levels were 1000 IU/mL, or 1210 ng/mL, with AFP levels ranging from 0.54–61830 IU/mL (0.6534 – 74814.3 ng/mL), which corresponds to the range of AFP levels found in HCC patients in the literature.

In this study, two examiners read the results of the abdominal CT scan and determined the abdominal CT scan score for HCC. The concordance between examiners in this study was very good. Most of the study subjects got the same score for abdominal CT scan results. The three subjects with significant differences in scores on the Bland-Altman Graph (Fig. 1) were due to differences of opinion in classifying HCC as massive or multilobulated.

CT with contrast is an imaging modality for screening and surveillance in high-risk populations. Hepatocellular carcinoma is a unique tumor among other malignancies because imaging can establish a definite diagnosis without a tissue diagnosis. In this case, a CT scan plays a role in establishing the diagnosis, determining the appropriate therapy, and monitoring the therapeutic response. In general, histological confirmation of malignancy is required only when imaging studies are uncertain.[18]

There have not been many studies examining the reliability of abdominal CT scan images in HCC. In a multicenter study involving 382 radiologists, the reliability of the 2014 LI-RADS (Liver Imaging Reporting and Data System) in HCC patients was also found to be quite good. In addition, the reliability of LI-RADS abdominal CT scan in hepatocellular carcinoma is not affected by familiarity with LI-RADS or the duration of post-residency practice.[19] This shows that the appearance of abdominal CT scans in the diagnosis and monitoring of HCC has high reliability even in radiologists who have no abdominal expertise.

There is a high correlation between abdominal CT scores and AFP levels in hepatocellular carcinoma. From the correlation graph, it can be seen that there is a positive correlation between abdominal CT scores and AFP levels. This shows that an increase in abdominal CT scores also represents an increase in AFP levels in HCC patients. This is appropriate because AFP levels generally increase with the progression of HCC, while higher abdominal CT scan scores in this study also indicate more disease progression.[12] From the partial correlation test results, only AFP levels were known to be significantly correlated with abdominal CT scan scores after controlling for variables of age, sex, and BMI. Meanwhile, the variables of age, sex, and BMI were not significantly correlated with abdominal CT scan scores in HCC patients.

This study concludes that there is a positive correlation between AFP levels and a CT scan of the abdomen in patients with hepatocellular carcinoma. There are still weaknesses in this study, including using a retrospective cross-sectional approach by taking data based on available medical records at a particular time so that clinical data and the course of the disease cannot be obtained entirely. The study was difficult to determine whether each abnormality contributes independently or together with tumor size on AFP levels in HCC due to the abdominal CT scan scoring in general. Therefore, improvement of research methodology using prospective study design is needed to avoid selection bias. CT scan results and AFP levels can also be measured under structured conditions to avoid confounding factors. Validating the scoring system in this study to be used in further research, both for diagnostic and prognostic purposes.

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Haemopoietic Actions of *Justicia secunda* Leaf Extracts in Mice

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Abstract

Objective: To evaluate the haemopoietic effects of *Justicia secunda* leaf ethanol, n-hexane, ethyl acetate, and n-butanol extracts in mice and compare these effects with the effects of standard antianaemic agents.

Methods: Sixteen groups of mice, six in each group, were used for the study. Anemia was induced in Groups 1 to 12 using 20 mg/kg i.p. phenylhydrazine (PHZ) daily for 2 days, followed by either ethanol, n-hexane, ethyl acetate or n-butanol extracts for 6 days. Groups 13 and 14 were induced for anemia and then received 200 mg/kg ferrous sulphate and vitamin B_{12} for 6 days. Group 15 (positive control) received 20 mg/kg PHZ i.p. only, while group 16 (negative control) was untreated. Blood was collected from the retro-orbital plexuses of the mice into EDTA-containing bottles on the 7th day and analyzed for hemoglobin (Hb) level, packed cell volume, mean cell hemoglobin concentration, and mean cell volume. Red blood cell, white blood cell, and platelet counts were also measured.

Results: The ethanol leaf extract of *J. secunda* significantly increased the hematological parameters of mice compared to the positive and negative controls (p<0.05). However, the n-hexane, ethyl acetate, and n-butanol extracts showed greater hemopoietic effects (p<0.001) than the ethanol extract and standard antianemic drugs. The extract of *J. secunda* leaf tended to stimulate erythropoiesis comparable to the standard antianemic drugs, especially the n-hexane.

Conclusion: *Justicia secunda* leaf extracts exert hemopoietic actions in mice, while the n-hexane extract shows greater haemopoietic activities than ferrous sulphate and vitamin B_{12}.

Keywords: Anaemia, haemoglobin, haemopoietic effect, *Justicia secunda*, phenylhydrazine

Introduction

Anemia is a condition in which the number of red blood cells (and consequently the oxygen-carrying capacity, hemoglobin) is insufficient to meet the body's physiologic needs. It results when the hemoglobin (Hb) concentration in the blood is lower than normal and affects about one-third of the world's population[1] and over 800 million women and children.[2] Anaemia in children is a major global public health concern and one of the major causes of childhood mortality, especially in developing countries.[3] It has significant consequences for human health as well as social and economic development in low-, middLe- and high-income countries.[4] The burden of anemia in some developing countries is 40% times higher than in most developed countries, with an average prevalence of 60 % among children aged 6–59 months having been reported in 27 Sub-Sahara African countries.[5]

Diagnosis of anemia is made when the Hb concentration falls below established cut-off values of 13 g/dL in men (15 years and above);

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12 g/dL in non-pregnant women (15 years and above); and 11 g/dL in pregnant women and children (6–59 months old).[6] When the hemoglobin concentration decreases, the ability of the blood to transport oxygen to tissues is compromised, leading to symptoms like fatigue, reduced physical work capacity, and shortness of breath, among others.[4] In two national representative cross-sectional surveys in Nigeria: the Nigeria Demographic and Health Survey (2018 NDHS) and the National Human Development Index (2018 NHDR), the prevalence of anemia among children in Nigeria was found to be 68.1%, with Zamfara State having the highest prevalence (84%), and Kaduna the least (50%).[7]

There are three main mechanisms underlying the development of anemia in mammals: ineffective erythropoiesis (when the body makes too few red blood cells), hemolysis (when red blood cells are destroyed), and blood loss. The most common contributors to anemia are nutritional deficiencies, diseases, and genetic hemoglobin disorders,[1] while the three top causes of anemia globally are iron deficiency, hemoglobinopathies, and malaria.[4] Iron deficiency is the most common cause of anemia (nutritional or otherwise) and is estimated to contribute to about 50% of all cases of anemia among non-pregnant and pregnant women, and 42% of cases in children under 5 years of age worldwide.[2] Haemolytic anemia is associated with oxidative stress within the erythrocytes,[8] with oxidative stress being involved in the aging and apoptosis of erythrocytes, thus inducing hemolysis.[9,10] Oxidative stress plays a role in anemia, which can manifest in the elevation of both oxidants and antioxidants (as a compensatory mechanism). It has been shown that levels of both would be ideal in arriving at a reasonable conclusion of oxidative status in anemia.[10] This concept is supported by the fact that hemolytic damage is accompanied by the generation of reactive oxygen species (ROS), glutathione depletion, Hb oxidation, and Heinz body formation in RBCs. Hemolytic agents have been reported to cause membrane lipid peroxidation and denaturation of cytoskeletal protein.[8] Factors associated with red blood cell destruction include infections, drugs, and hemoglobinopathies, which lead to reduced ability of blood to carry oxygen.[11] Evidence has shown that up to 130 drugs can induce hemolytic anemia through several mechanisms.[12] Phenylhydrazine treatment has been shown to induce changes in various blood cell counts causing haemotoxicity and consequently leading to hemolytic anemia;[13] hence its use in the induction of anemia in experimental models.

For many years, medicinal plants were the only sources of treatment for diseases in humans and many of today's drugs have been isolated from medicinal plants. Herbal remedies have relied heavily on the use of natural products as active ingredients.[14] The WHO reported that up to 80% of the population in Africa depends on traditional medicine to help meet their healthcare needs.[15] A number of natural products, including herbs, are widely used in folk medicine to prevent and/or alleviate anemia.[16] *Justicia Secunda* is an evergreen perennial plant with stems that sometimes become more or less woody, growing up to 90–200 cm tall. The plant comprises almost 250 genera, with 2500 species, and is harvested from the wild bush for local use as medicine. The plant species are widespread in tropical regions and are poorly represented in temperate regions. The leaf decoction of *J. Secunda* is used for the treatment of various ailments including anemia, fever, malaria, cough, and cold.[17] This study, therefore, was set to evaluate the basis for the use of *J. Secunda* leaf for the treatment of hemopoietic disorders.

Methods

Healthy albino mice (both male and female) weighing 18–30 g were sourced from the Animal House Facility of the Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Agulu Campus. The animals were housed in cages and fed with commercial rat pellets and tap water at the Pharmacology Laboratory of the Faculty of Pharmaceutical Sciences of our University, where the study was carried out, from October to December 2019. Before administration of the extract, the animals were acclimated to laboratory conditions for two weeks. The animals were allowed access to food and water *ad libitum.* The study protocol was approved by Nnamdi Azikiwe University Teaching Hospital, Ethics Committee, Nnewi, Nigeria NAUTH/CS/66/vol.11/187/2018/122).

Justicia Secunda leaves were collected from a local farm at Abakiliki, South-East Nigeria. The plant was identified by a plant taxonomist, Mr. A. Ozioko of 110 Aku Road, Nsukka, Nigeria. A voucher specimen of the plant was deposited at the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Nigeria,

Nsukka, Nigeria, with the voucher number *Justicia Secunda*-interceded/29648. Standard anti-anemic agents, ferrous sulfate (Reagan Remedies Ltd, Owerri, Nigeria) and vitamin B_{12} (Mason Vitamins Inc. Miami, USA), and the anemia-inducing agent phenylhydrazine (Sigma, Steinheim, Switzerland) were all bought from Index Pharmacy, Nnewi, Nigeria. All the drugs and chemicals used in the study were of analytical grade.

The plant material was extracted in four different solvents by agitation extraction method, which involved successive extraction with solvents of increasing polarity, from non-polar n-hexane to more polar ethanol. This was to ensure the extraction of a wide polarity range of compounds as well as choosing the solvent that will give a higher percentage yield of the extract. This process was done by weighing 1,000 g of the pulverized plant leaf into an Erlenmeyer flask containing 80% ethanol in water for 72 h, using a solid/liquid ratio of 1:10. With intermittent shaking every 2 min in an orbital shaker. This was thereafter filtered with Whatman No.1 filter paper. The filtrate was concentrated using a rotary evaporator at 40°C. The paste weighed 85.4 g and was stored in a refrigerator until use. The phytochemical study was carried out with ethanol extract, using standard methods as recommended by Evans.[18] All measurements were taken in triplicates.

The median lethal dose (LD_{50}) was determined in the ethanol extract, using the up and down procedure (UDP) in accordance with Guideline No. 425 of the Organization for Economic Cooperation and Development (OECD).[19] The dose of the extract that reversed anemia in the mice was determined by calculating the median effective dose (ED_{50}), using the method of Miller and Tainter as described by Milan *et al*.[20] The experiment was conducted with 30 anemic mice, with anemic mice being mice with Hb<11.5 g/dL. Briefly, the mice were randomly assigned to 5 groups of 6 mice per group. Each group received a single oral dose of either of the extracts at 4, 8, 16, 32, or 64 mg/kg for 7 days. After

Table 1 Effect of *J. Secunda* Leaf Extracts on Hemoglobin Level (g/dL) in Mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	14.05±0.97	10.20±0.98*	12.30±0.70*	20.80	0.001
MD	13.60±0.78	11.30±2.19	12.33±2.24	2.81	0.142
HD	13.95±1.39	10.38±0.48*	13.75±1.12#	18.73	0.018
n-hexane extract (mg/kg)					
LD	13.58±1.15	9.73±1.65*	12.53±1.46*	9.51	0.019
MD	14.85±0.58	10.38±1.18*	12.80±0.89*	46.13	0.001
HD	13.13±1.49	11.03±0.83	15.13±0.15+#	11.08	0.012
Ethyl acetate extract (mg/kg)					
LD	13.80±1.27	10.60±1.99*	12.20±0.39*	7.01	0.025
MD	15.00±0.76	10.38±0.78*	11.78±1.88*	20.27	0.004
HD	13.97±0.81	9.72±0.88*	13.48±0.85#	43.08	0.002
n-butanol extract (mg/kg)					
LD	13.98±0.76	10.36±1.61*	11.53±0.67*	14.51	0.003
MD	14.12±0.52	9.52±1.20*	13.43±1.69*	20.84	0.001
HD	13.94±0.40	8.70 ± 0.53*	13.70±2.10#	34.95	0.011
$FeSO_4$ (0.2 mg/kg)	15.70±0.66	8.90±1.39*	13.80±0.88#	21.50	0.044
Vit B_{12} (100µg)	14.60±0.66	9.10±1.32*	13.40±1.10#	31.17	0.035
Negative control	14.90±1.66	15.34±1.17	14.30±1.34	1.23	0.340

LD=low dose; MD=median dose; HD=high dose; *Significantly lower than baseline value ($p<0.05$); +Significantly higher than baseline value ($p<0.05$); #Significantly higher than the induction value ($p<0.05$)

Table 2 Effect of *J. Secunda* Leaf Extracts on Packed Cell Volume (L/L) in mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	48.98±2.54	34.25±2.95*	38.90±3.32*	35.05	0.034
MD	48.92±2.77	34.96±4.04*	39.35±7.05*	11.73	0.009
HD	46.20±3.20	30.20±14.52*	46.10±6.60#	20.82	0.014
n-hexane extract (mg/kg)					
LD	44.97±3.54	32.30±2.31*	40.10±7.07*#	14.35	0.036
MD	49.10±1.86	33.93±3.07*	41.70±4.48*#	33.83	0.010
HD	43.33±5.98	33.70±2.24*	49.57±1.46+#	11.54	0.016
Ethyl acetate extract (mg/kg)					
LD	46.35±4.05	32.70±8.11*	40.75±1.46*#	8.69	0.016
MD	49.90±2.92	33.28±1.93*	39.65±5.51*#	23.36	0.004
HD	48.70±2.03	31.20±3.94*	45.90±1.28#	52.10	0.019
n-butanol extract (mg/kg)					
LD	46.62±2.31	30.28±5.73*	37.93±1.05*#	27.51	0.004
MD	45.70±1.62	29.60±2.25*	44.50±4.10#	48.60	<0.001
HD	46.40±1.57	26.40±4.32*	44.70±5.78#	37.04	0.006
$FeSO_4$ (0.2mg/kg)	51.90±2.22	31.80±1.32*	46.70±2.71#	19.47	0.049
Vit B12 (100µg)	47.80±2.20	28.90±6.38*	44.90±5.28#	52.30	0.010
Negative control	49.34±4.67	52.44±4.14	50.50±4.49	0.53	0.551

LD=low dose; MD=median dose; HD=high dose; *Significantly lower than the baseline value ($p<0.05$); +Significantly higher than the baseline value ($p<0.05$); #Significantly higher than the induction value ($p<0.05$)

the 7-day treatment period, the hemoglobin concentration of each mouse was determined for the different groups. Mice with Hb≥11.5 g/dL were considered as having their anemia reversed.

Ninety-six healthy albino mice of different sexes, weighing 28–30g, were divided into 16 groups of 6 mice per group. Animals in groups 1–12 were treated with 20 mg/kg (i.p.) phenylhydrazine (PHZ) for 2 days, and from the 3rd day onwards the animals were administered 2.7 mg/kg (p.o.) (low dose, LD), 8.3 mg/kg (medium dose, MD) and 24.9 mg/kg (high dose, HD) of ethanol, n-hexane (NH), ethyl acetate (EA) and n-butanol (NB) extracts of *J. Secunda* leaf for 6 days. The animals in Group 13 were treated with 20 mg/kg (i.p.) PHZ for 2 days and thereafter 200 mg ferrous sulfate, while the Group 14 animals received 20 mg/kg (i.p.) PHZ for 2 days followed by 100 µg vitamin B_{12}. The positive control (Group 15) received 20 mg/kg (i.p.) PHZ only, while the negative control (untreated) (Group 16) received only feed and water. All the animals in the positive control (Group 15) died on the 3rd day of treatment.

On the 7th day of treatment, 1ml of blood was collected from the retro-orbital plexus of the animals into ethylenediaminetetraacetic acid (EDTA)-containing bottles. The samples were analyzed for hematological parameters using a hematology automated analyzer machine (Mindrays, Model BC-2800Vet, China). The hematological parameters analyzed were hemoglobin, packed cell volume, total red blood cell count, white blood cell count, mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet count. All the parameters were estimated thrice.

Data were presented as mean ± standard deviation and analyzed using the one-way analysis of variance (ANOVA), followed by Bonferroni's multiple comparison (post-hoc) test. Statistically significant levels were determined at $p<0.05$.

Table 3 Effect of *J. Secunda* Leaf Extracts on Mean Corpuscular Hemoglobin Concentration in Mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	28.92 ± 0.53	29.98 ± 1.59	30.35 ± 0.29	2.58	0.171
MD	29.34 ±0.75	33.94 ± 1.47^{+}	31.88 ± 1.05**	20.48	0.004
HD	29.95 ± 1.04	34.18 ± 0.77^{+}	30.53 ± 2.04**	13.04	0.009
n-hexane extract (mg/kg)					
LD	30.28 ± 1.50	35.28 ±3.37	31.70 ± 1.94	5.72	0.055
MD	30.48 ±0.70	33.28 ± 3.15	31.90 ± 1.56	2.77	0.187
HD	29.83 ±0.67	32.70 ± 2.01^{+}	30.50 ± 0.70**	6.61	0.048
Ethyl acetate extract (mg/kg)					
LD	29.48 ± 0.67	32.84 ± 2.12^{+}	30.18 ± 0.51**	9.36	0.012
MD	30.40 ± 0.70	31.55 ± 1.10^{+}	29.63 ± 0.87**	4.93	0.035
HD	28.86 ± 0.63	31.70 ± 1.26^{+}	29.63 ± 1.26**	9.60	0.006
n-butanol extract (mg/kg)					
LD	29.95 ± 1.01	34.84 ± 4.91	30.00 ± 1.14	5.14	0.101
MD	30.85 ± 0.51	32.20 ± 1.84	30.10 ± 1.15	3.27	0.105
HD	30.00 ± 1.49	33.00 ± 3.65	30.50 ± 0.70	1.95	0.223
$FeSO_4$ (0.2mg/kg)	30.40 ± 0.00	28.10 ± 1.32	29.90 ± 0.66	4.98	0.167
Vit B_{12} (100µg)	30.00 ± 0.44	30.20 ± 1.32	30.50 ± 0.88	4.77	0.677
Negative Control	30.20±0.34	29.20±0.26	29.42 ± 0.83	4.22	0.086

LD = low dose; MD = median dose; HD = high dose; $^{+}$Significantly higher than baseline value ($p < 0.05$); **Significantly lower than the induction value ($p < 0.05$)

Results

The qualitative phytochemical analysis showed that *J. Secunda* ethanol leaf extract contains saponins ++, tannins ++, flavonoids +, alkaloids +, terpenoids +, carbohydrate +, and reducing sugars +. The quantitative analysis showed that saponins had the highest concentration of 9.2 %, followed by tannins (9.0 %) and flavonoids (7.0 %), while alkaloids had the least concentration (2.4%).

The ED_{50} of *J. Secunda* ethanol leaf extract was determined as 8.3 ± 3.2 mg/kg (C.I.: 5.1-11.5 mg/kg). This value was then used to determine the doses for the study. Administration of 2000 mg/kg (p.o.) of the extract produced no death or any signs of toxicity, so the LD_{50} was taken as > 2,000 mg/kg, following the UDP for LD_{50} determination. The therapeutic index (TI) was subsequently calculated to be 240.96.

The Hb levels of the PHZ-induced anemic mice and those that were treated with LD of ethanol extract, and LD and MD of the NH, EA, and NB extracts were significantly lower than the baseline values (Table 1). Treatment of the anemic mice with LD and MD of all the extracts resulted in a non-significant increase ($p>0.05$) in Hb levels of the animals compared to the induction levels. However, the Hb levels of the animals treated with HD of the extracts were significantly increased ($p<0.05$) in comparison with the induced animals, just like the standard agents (ferrous sulfate and vitamin B_{12}) (Table 1). Treatment with HD of NH extract, however, caused a significant increase in Hb level (15.13 ± 0.15) compared to the baseline value (13.13 ± 1.49) ($p=0.012$).

The PCV of the anemic mice and those

Table 4 Effect of *J. Secunda* leaf Extracts on Red Blood Cell Count (10^6cells/mm^3) in Mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	8.28 ± 0.19	6.63 ± 0.65*	5.80 ± 0.65*	50.04	0.004
MD	3.46 ± 0.50	6.16 ± 1.00*	5.23 ± 0.86*	14.20	0.001
HD	7.83 ± 0.62	5.70 ± 1.02*	7.60 ± 0.73#	15.84	0.038
n-hexane extract (mg/kg)					
LD	7.38 ± 0.98	4.10 ± 0.93*	5.73 ± 0.73*	15.10	0.002
MD	7.82± 0.58	5.53 ± 0.62*	5.85 ± 0.38*	82.40	0.043
HD	7.35 ± 1.13	5.55 ± 0.34*	8.30 ± 0.10#	10.60	0.020
Ethyl acetate extract (mg/kg)					
LD	8.08 ± 0.63	5.58 ± 1.41*	6.68 ± 0.88*	8.48	0.010
MD	8.54 ± 0.67	5.48 ± 0.69*	6.95 ± 0.76*	21.23	0.003
HD	7.64 ± 0.31	4.78 ± 0.73*	7.70 ± 0.26#	68.70	0.019
n-butanol extract (mg/kg)					
LD	7.87 ± 0.40	4.94 ± 0.96*	6.73 ± 0.86*	21.60	0.008
MD	8.12 ± 0.24	4.65 ± 0.55*	7.15 ± 1.07#	34.90	0.001
HD	7.70 ± 0.23	4.15 ± 0.26*	8.20 ± 0.90#	85.83	0.006
$FeSO_4$ (0.2mg/kg)	6.93 ± 1.54	4.77 ± 0.88	6.27 ± 0.66	19.17	0.159
Vitamin B_{12} (100µg)	6.60 ± 0.88	4.90 ± 0.66	6.50 ± 0.88	4.16	0.194
Negative control	8.48±0.59	8.52±0.76	7.84 ± 1.91	0.45	0.552

LD=low dose; MD=median dose; HD=high dose; *Significantly higher than baseline value ($p<0.05$); **Significantly lower than the induction value ($p<0.05$)

treated with LD and MD of the extracts were significantly lower ($p<0.05$) than the baseline group (Table 2). There was a statistically significant increase ($p<0.05$) in the PCV of the animals treated with the HD ethanol extract, and LD, MD, and HD of the other extracts in comparison with the anemic mice, in the same manner as the standard agents. Again, treatment with HD of NH extract caused a significant increase ($p=0.016$) in PCV (49.57±1.46) compared to the baseline value (43.33±5.98).

There were significantly higher ($p<0.05$) MCHC in the MD and HD induction values of the ethanol extract than the baseline values (Table 3). Treatment with MD and HD ethanol and HD n-hexane and LD, MD, and HD ethyl acetate extracts resulted in a significant decrease in MCHC of mice in comparison with the values of the induced mice. Also, the MD and HD induction group of the ethanol, and the HD n-hexane and LD, MD and HD ethyl acetate extracts of the induction group showed a statistical increase ($p<0.05$) in MCHC compared to the baseline values (Table 3).

The RBC counts of the anemic mice and those treated with LD and MD of the extracts were significantly lower ($p<0.05$) than those of the baseline group, but the RBC counts of the animals treated with HD of the extracts were increased significantly ($p<0.05$) when compared with the RBC count of the induced animals (Table 4). Treatment of the anemic mice with the standard agents caused no significant differences in the RBC count (Table 4). The effect of the extracts on the

Table 5 Effect of *J. Secunda* Leaf Extracts on White Blood Cell Count (10^9/L) in Mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	4.54 ± 0.27	3.05 ± 0.39*	3.87 ± 0.59#	23.41	0.013
MD	3.46 ± 0.50	4.90 ± 2.10	4.45 ± 0.40	1.68	0.271
HD	4.30 ± 0.53	3.10 ± 0.81	4.00 ± 0.67	4.70	0.165
n-Hexane extract (mg/kg)					
LD	4.28 ± 0.30	3.65 ± 1.30	3.57 ± 0.57	1.17	0.326
MD	3.58 ± 0.54	2.25 ± 0.72*	4.18 ± 0.59#	11.33	0.028
HD	3.52 ± 0.68	3.28 ± 0.98	3.00 ± 0.42	0.45	0.340
Ethyl acetate extract (mg/kg)					
LD	3.30 ± 1.32	4.10 ± 1.54	3.00 ± 0.44	2.55	0.182
MD	4.10 ± 0.88	2.80 ± 0.66	2.70 ± 0.44	23.19	0.079
HD	4.00 ± 0.88	2.80 ± 0.66*	3.90 ± 1.32#	15.86	0.009
n-butanol extract (mg/kg)					
LD	3.75 ± 0.28	3.84 ± 0.98	2.86 ± 0.50	2.82	0.206
MD	3.78 ± 0.73	3.15 ± 0.57	3.60 ± 0.49	1.22	0.329
HD	2.70 ± 0.44	2.90 ± 0.66	4.50 ± 0.00	94.66	0.0002
$FeSO_4$ (0.2mg/kg)	3.40 ± 1.10	4.90 ± 0.44	4.40 ± 0.44	1.93	0.341
Vit B_{12} (100µg)	4.10 ± 0.66	3.20 ± 0.66	4.60 ± 0.66	5.146	0.163
Negative control	4.34±0.48	2.98±0.64*	4.33±0.35#	11.06	0.003

LD=low dose; MD=median dose; HD=high dose; *Significantly higher than baseline value ($p<0.05$); **Significantly lower than the induction value ($p < 0.05$)

MCV showed that only the HD ethanol extract resulted in a significant increase (p=0.011) in the MCV of the treated mice (59.03±1.04 f/L) when compared with the anemic mice (56.15±1.29 f/L).

The LD ethanol, MD n-hexane, and HD ethyl acetate extracts all had a significant increase in the WBC counts of the animals in comparison with those of the animals induced with anemia (Table 5). Platelet counts of the animals in the baseline, induction, and treatment groups did not differ statistically from one another, except in the LD and MD ethanol extract, which caused a significant decrease (p<0.05) in comparison with the baseline value. The LD ethanol extract treatment also caused a significant increase (p=0.014) in the platelet count (1334.0±348.90) in comparison with the anemic mice (1039.00±220.20) (Table 6).

Discussion

This study assessed the hemopoietic properties of *J. Secunda* leaf extracts in mice using ethanol, n-hexane, ethyl acetate, and n-butanol solvents. The findings showed that *J. Secunda* leaf contained phytochemicals like saponins, tannins, flavonoids, and alkaloids. The different biological activities and promising drug properties are the consequence of the unique chemical diversity that has arisen in natural products.[21] The presence of these phytochemicals in the extract is in agreement with the findings of Yamoah and co-workers, which also found that *J. Secunda* contained tannins, saponins, alkaloids, flavonoids, glycosides, and sterols.[22] Our findings did not reveal the presence of glycosides and steroids which were reported by Yamoah.

Table 6 Effect of *J. Secunda* Leaf Extracts on Platelet Counts (10^9/L) in Mice

Group	Baseline	Induction	Treatment	F	p-value
Ethanol extract (mg/kg)					
LD	1850.00±140.60	1039.00±220.20*	1334.0±348.90*#	14.55	0.014
MD	1622.00±207.20	1041.00±159.20*	1100.0±118.10*	21.19	0.000
HD	1174.00±81.85	983.70±69.10	1334.0±214.60*	5.74	0.054
n-hexane extract (mg/kg)					
LD	1174.00±140.90	853.00±490.80	957.0±106.90	1.57	0.265
MD	1025.00±121.50	1063.00±101.80	1179.0±153.90	1.83	0.229
HD	1135.00±451.80	1158.00±237.40	1031.0±190.10	0.12	0.767
Ethyl acetate extract (mg/kg)					
LD	1408.00±410.40	1011.00±41.36	1169.0±152.70	3.24	0.146
MD	977.30±75.29	1113.00±139.80	989.30±61.45	2.75	0.148
HD	1046.00±85.02	1276.00±177.80	1115.0±44.23	4.41	0.106
n-butanol extract (mg/kg)					
LD	973.70±157.50	1020.00±364.60	987.0±65.02	0.10	0.782
MD	1025.00±112.60	1191.00±181.70	1129.0±150.50	1.67	0.237
HD	986.00±65.22	1034.00±71.65	976.0±166.60	0.39	0.561
$FeSO_4$	1329.30±291.94	1194.25±299.86	1212.6±405.02	0.13	0.882
Vit B_{12}	1396.00±359.48	1024.8±49.94	1274.6±205.92	1.67	0.374
Neg control	1136.00±125.90	1225.00±203.00	1156.0±154.70	0.42	0.561

LD=low dose; MD=median dose; HD=high dose; *Significantly higher than baseline value ($p<0.05$); **Significantly lower than the induction value ($p<0.05$)

The differences in the phytochemical contents could be attributed to the environmental conditions, such as soil fertility, pH, water supply, climate, and seasonal variations, at the different geographical locations in which the plant material was grown.

The ED_{50} of the extract (i.e. dose that was able to restore Hb level to ≥11.5 g/dL in 50 % of the anemic mice) was 8.3±3.2 mg/kg. This shows that the plant extract has a very potent hemopoietic property. The acute oral toxicity test revealed that the extract, at a dose of 2000 mg/kg, was not able to cause death or any sign of toxicity after 14 days of exposure, giving a therapeutic index of over 240. This is an indication that the extract has a very wide safety margin and is practically non-toxic. With the economic downturn in society, some patients are unable to afford the conventional drugs used in the management of anemia, coupled with their attendant adverse effects. In contrast, herbal medicines used in therapy are comparatively cheap, readily available, and thought to be less toxic than conventional drugs. However, the use of herbal medicine extracts without safety evaluation could be noxious.

The hemopoietic potentials of the extract were demonstrated by the restoration of some of the hematological parameters to normal levels, after treatment with the various doses of *J. Secunda* leaf extracts in as short as 6 days. Essentially, treatment with high dose n-hexane extract raised the Hb and PCV levels of the animals significantly in comparison with both the induction and baseline values. It is noteworthy that the standard hemopoietic drugs (ferrous sulfate and vitamin B_{12}) were not able to raise the Hb and PCV values of the animals as much as the high-dose n-hexane extract. This effect may be due to the presence of phytochemicals in

the plant extracts. Bigoniya *et al*.[23] reported good anti-anemic and hematopoietic activities in *Wrightia tinctoria* bark methanolic extract, which has a rich presence of flavonoid and polyphenolic compounds. Some medicinal herbs used in traditional medicine for the treatment of anemia in Cote d'Ivoire revealed that *J. Secunda* had a Fe content of 26.6 mg/100 g of the extract, while the stem bark of *Khaya senegalensis* (Mahogany), a popular haematinic, had 33.3 mg/100 g.[17] Iron forms the nucleus of the iron-porphyrin haeme ring, and together with globin chains forms Hb. This may be responsible for the hematinic properties of *J. Secunda* in mammals.[22] The exact mechanisms by which the extracts exhibited the reported effect need further investigation. Many plant extracts have been found to raise the Hb levels of mice and thus, used for the treatment of anemia.[17] ExpectedLy, there were no significant differences between the MCHC values of the treatment and baseline groups and also those of the standard drugs, since there were corresponding changes in the Hb and PCV values across the different study groups. There were no significant changes in the white blood cell and platelet counts of the treatment and baseline groups in all the extracts employed. It is plausible that *J. Secunda* leaf extracts do not exert thrombocytic and leucocytic effects.

This study was designed to provide scientific evidence for the plausible hemopoietic action of *J. Secunda* leaf by the local populace. We have been able to prove that the plant extracts possess hemopoietic effects as claimed. Similar findings were also found with the leaf and stalk extract of *Beta vulgaris* by Gheith and El-Mahmoudy.[24] Stevens and co-workers have reported that inadequate progress has been made on anemia in women aged 15–49 years, to meet the World Health Assembly global nutrition target to halve the prevalence of anemia by 2030 and that the prevalence of anemia in children had also remained high.[25] If this target of reducing the prevalence of anemia must be met, alternative treatment approaches, like the use of medicinal herbs, would need to be employed; on this premise, *J. Secunda* finds its relevance.

From the findings, the extracts of *J. Secunda* leaf exert hemopoietic action in PHZ-induced anemic mice, by causing an increase in Hb concentration, and thus justifies the use of the plant leaf in the management of anemia. The n-hexane extract showed better hemopoietic activity than the standard haematinics, ferrous sulfate, and vitamin B_{12}. These results show that *J. Secunda* could be a good and promising source for pharmaceutical preparations with hemopoietic actions and associated conditions. The limitations to the study were: firstly, the study was carried out with extracts only. Further studies are required to isolate and characterize the active molecules responsible for the actions. Also, the design was an animal study, which does not always give similar results to man. Relevant safety data assays, followed by clinical studies are recommended before the use of the extracts in man.

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High-risk Neuroblastoma in Young Adult and Long Term Survival with Multimodal Therapy: A Case Report

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Abstract

Objective: To present a case of high-risk, stage four neuroblastoma in a 20-year-old woman who survived more than 21 months with the multimodal therapy.

Methods: A case of high-risk, stage four neuroblastoma in a 20-year-old woman who survived more than 21 months with multimodal therapy is reported. The patient initially received neoadjuvant chemotherapy according to the Turkish Pediatric Oncology Group of Neuroblastoma, along with multiple doses of radiotherapy. After two cycles of induction chemotherapy, she successfully underwent tumor debulking surgery.

Results: With the multimodal therapy, patient remains in complete remission state and stable disease of the remaining lesions is observed in this patient.

Conclusions: Neuroblastoma is a rare disease in adults and associated with a high number of mortality. Early and accurate diagnosis and multimodality of treatments are important to achieve disease control. Long term follow up is necessary for such patients.

Keywords: High-risk Neuroblastoma, long term survival, young adult

Introduction

Neuroblastoma is an embryonal neoplasm of the sympathetic nervous system arising from the neural crest. The incidence of neuroblastoma peaks in infancy and childhood. Meanwhile, in adults, only one case in ten million populations was reported.[1] It has a unique clinical and biological heterogeneity of the tumors. Adolescent neuroblastoma often has a more indolent and chemo-resistant profile, associated with dismal survival.[2] The majority of neuroblastoma cases in adults showed high mortality within five years of follow-up.[3] There is no standard treatment protocol for adult neuroblastoma, and the treatment protocol still uses pediatric guidelines.[1] We present a rare case of high-risk neuroblastoma in 20-year-old women who had long-term disease stability and survival for more than 5 years with multimodal therapy.[4]

Case

A 20-year-old woman presented to our hospital with a one-month history of severe pain in the lump on her neck's left side. She lumped for the last eight years; it was not visible yet palpable at first and it had been slowly growing to approximately a grape-sized around six years ago. A histopathological finding from the left cervical lymph node performed six years ago revealed neuroblastoma, with immunohistochemical (IHC) staining positive

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Table Chemotherapy regimens on Turkish Pediatric Oncology Group Neuroblastoma 2003[1]

Chemotherapy	Drugs	Schedule
Induction cycles A3–1 cycle 15–19 July 2019	Vincristine	1.5 mg/m^2/day, D 1 and 5, IV push
	Ifosfamide	1.8 g/m^2/day, D 1-5, IV continues infusion
	Dacarbazine	250 mg/m^2/day, D 1-5, IV 30 min
	Adriamycin	20 mg/m^2/day, D 1-3, IV over 4 h
A5–1 cycle 15–19 August 2019	Cisplatin	30 mg/m^2/day, D 1-5, IV continues infusion
	Cyclophosphamide	300 mg/m^2/day, D 1-5, IV over 1 h
	Etoposide	150 mg/m^2/day, D 4 and 5, IV 1 h

for expression of *CD56*, chromogranin-A, and synaptophysin. Although she had been suffering from the lump for the last eight years (May 2014), she did not seek medical treatment. Instead, she preferred traditional medicine, dealing with herbal therapies.

She underwent twice positron emission tomography (PET), the first in 2016 and the second in 2017. The first PET showed 3.79 x 1.44 cm hypermetabolic multiple lymph nodes chains at the left superior jugular to left supraclavicular, and a hypermetabolic lesion at the body of the second thoracic vertebra, with the maximum standardized uptake values (SUV), was 27 (Fig. 1A, B). The second PET in 2017 showed advanced disease progression and a larger left neck soft tissue mass sized 9.3 cm x 8.4 cm x 10.0 cm with an SUV maximum

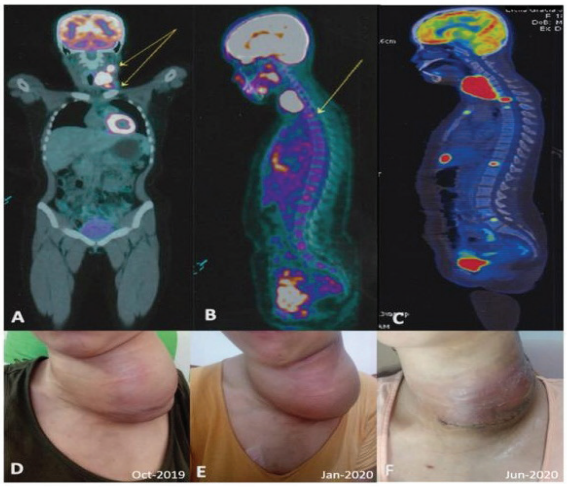

Fig. 1 (A-F): Coronal and axial views of patient's PET in 2014 (A and B); restaging PET showing progressive disease three years later (C). Clinical views after the first radiotherapy, revealed a left-sided neck mass sized 12 cm x 10 cm x 10 cm (D), after two cycles of temozolomide, sized 10 cm x 8 cm x 8cm (E), and after debulking surgery (F)

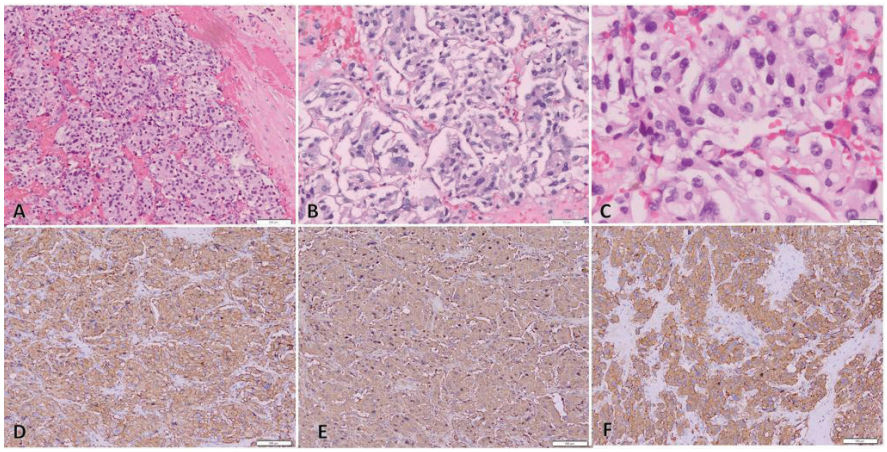

Fig. 2 (A-F). Hematoxylin and eosin (H&E) staining from tissue biopsy (A) 100x, (B)200x, and (C)400x, showing clusters and packets of small neoplastic cells forming Homer-Wright rosettes, with fairly dispersed chromatin, inconspicuous nucleoli, and indistinct cytoplasm. CD56 (D), chromogranin (E), and synaptophysin (F) IHC stains are positive in this tissue

score of 44.6 (Fig. 1C). Medially the mass slightly compresses the trachea lumen, with the suspect of thyroid gland infiltration; laterally compressing left submandibular gland; inferiorly extending into 2nd level thoracic inlet, posteriorly extending with 6-7th cervical – first thoracic vertebra. There were also diffuse metastatic foci, including supraclavicular and anterior mediastinum lymph nodes, pulmonary, liver, pancreas, and over axial to the appendicular skeleton.

Physical examination revealed approximately 10 cm x 15 cm x 8 cm mass on her left neck. The mass was firm, immobile, tender, and had a lobulated surface. There was venectation of the skin over the lump, chest, and abdominal wall. Other physical findings were unremarkable, and all laboratory results were within normal limits. The histopathologic examination and immunohistochemical staining, which confirmed the diagnosis of neuroblastoma, are shown in Fig. 2. The patient has been diagnosed with high-risk stage four neuroblastoma.

A neck CT was performed before chemotherapy began in June 2019, and showed a single, large, left neck tumor, size 12.67 cm x 10.68 cm x 10.42 cm, involving its adjacent tissues, multiple cervical lymphadenopathies, multiple bone destructions, and pulmonary metastases. Finally, in July 2019, the patient received a chemotherapy regimen according to the Turkish Pediatric Oncology Group of Neuroblastoma with one cycle of induction A3 and A5 (Table 1), along with zoledronic acid (4 mg intravenous, qd). After two cycles of induction chemotherapy, the tumor size reduced (Fig. 1D) and she had a stable disease. The therapy was followed by radiotherapy of 40 Gy in 20 daily fractions over four weeks. Waiting for debulking surgery, the patient received two cycles of temozolomide 200 mg/m^2/day (240 mg) per os (PO) for days 1–5, every 28 days (Fig. 1E). This treatment is based on research made by Zhu *et al*.[5] In June 2020, the patient underwent successful tumor debulking surgery (Fig. 1F). Afterward, the patient was started on 20 cycles of postoperative radiotherapy. The patient is under follow-up, after 21 months she is in complete remission of the primary neuroblastoma and stable disease of the base of the remaining lesion on clinical examination.

Discussion

Arising from primitive neural crest cells, neuroblastoma incidence peaks in infancy.[2] There are only <5% of neuroblastoma cases diagnosed after ten years of life. Even though older patients with neuroblastoma (>18 months) have a more indolent disease course, they are associated with poor prognosis.[6] Esiashvili *et al*. reported a 45.9% and 36.3% survival rate in adults (>20 years old) with neuroblastoma for three and five years, respectively.[7] Primary neuroblastoma could occur anywhere along all sympathetic nerve chains.[3] Moreover, head and neck neuroblastoma are rare but more common

in older age (>17 years old). A study by Kauffman *et al*.[1] reported only 3.9% out of 4.500 of their patients presented with head and neck neuroblastoma. Interestingly, they have a more favorable prognosis when compared with the other tumor locations. Neuroblastoma can be classified into low-risk, intermediate, and high-risk groups based on the patient's age at diagnosis, tumor stage, histopathology examination using The International Neuroblastoma Pathology Classification (INPC) system, deoxyribonucleic acid (DNA) index, and the presence of MYCN amplification.[2] According to the classification, our patient with 20 years of age at diagnosis and the stage-4 tumor is included in the high-risk group. Neuroblastoma is rare in adults, but it is important to consider it as one differential diagnosis from other small round blue cell tumors.[3] In our case, we consider lymphoma, small cell carcinoma, rhabdomyosarcoma, and primitive neuroectodermal tumor (PNET) as the differential diagnosis. It was subsequently excluded based on IHC findings: The lack of staining for lymphoid marks CD20, CD3, and CD30 rules out lymphoma, while lacking cytokeratin's expression (MNF116, Cam5.2) excludes small cell carcinoma. Furthermore, the absence of desmin staining rules out rhabdomyosarcoma, and the lack of CD99 expression argues against primitive neuroectodermal tumor (PNET) in favor of neuroblastoma.

The treatment regimens used for children with high-risk neuroblastoma have four main components: (1) induction chemotherapy, (2) local control, (3) consolidation, and (4) maintenance therapy.[2] Most currently employed induction regimens for high-risk neuroblastoma utilize a combination of anthracyclines, platinum-containing compounds, alkylating agents, and topoisomerase-II inhibitors. The most recently completed protocol for high-risk neuroblastoma treatment employed by the Children's Oncology Group (COG) utilized six cycles of induction chemotherapy, including the combination of topotecan and cyclophosphamide for the first two induction cycles, cisplatin, and etoposide for cycles 3 and 5 and cyclophosphamide, vincristine and doxorubicin for cycles 4 and 6.[8] European protocols have utilized COJEC/ OPEC regimens, which include cisplatin (C), vincristine (O), carboplatin (J), etoposide (E), and cyclophosphamide (C) or vincristine (O), cisplatin (P), etoposide (E), and cyclophosphamide (C). In a recent study, a regimen using 'rapid' COJEC aiming to increase treatment dose intensity was evaluated. Rapid COJEC was administered in 8 cycles, separated by ten-day intervals, allowing completion of induction within 70 days from administering the first drug. Rapid COJEC has been incorporated into the standard treatment regimen for these children with high-risk neuroblastoma.[9] Myeloablative chemotherapy with autologous stem cell rescue (ASCR) is recommended for consolidation therapy.[2,10]

Local control is a critical component of high-risk neuroblastoma therapy to prevent the local recurrence of the disease. Local control treatment modalities include surgical resection, generally after 4–6 cycles of induction therapy, external beam radiation to the primary site, and other active, residual disease sites.[2] Radiotherapy was recommended for the primary and all bulky metastasis following induction chemotherapy and surgery, and the total dose was modulated by age (25 Gy ≤ 2 years and 35 Gy > 2 years).[11] Patients with high-risk neuroblastoma typically enter the maintenance phase of therapy after induction chemotherapy, surgical resection, myeloablative therapy with ASCR, and radiation therapy.[2]

Our patient received two cycles of induction chemotherapy according to the Turkish Pediatric Oncology Group Neuroblastoma 2003 regimen: induction A3: vincristine, ifosfamide, dacarbazine, adriamycin for five days and A5: cisplatin, cyclophosphamide, etoposide for five days.[11] We chose this regimen because of the availability of drugs in our hospital. She had a stable disease after two cycles of chemotherapy. We did not continue with myeloablative therapy with autologous stem cell rescue because of toxicity and limited hospital resources. She received local control with external beam radiotherapy. After radiotherapy, we give her temozolomide. Temozolomide was considered because of the tendency of mass enlargement after radiotherapy. Temozolomide has been recommended for second-line chemotherapy for neuroblastoma either as a single agent or combined with topotecan or irinotecan, or etoposide. This temozolomide-based regimen has a response rate of around 47% to 73%.[12]

Patients with high-risk neuroblastoma who do not respond to induction therapy are more difficult subgroups to treat, with long-term survival rates of less than 20%.[2] Tumor response rates are also lower in adolescents and adults, who often have indolent, chemoresistance tumors compared to tumors

in younger children that tend to be more responsive to chemotherapy.[6] However, our patient has a stable disease and a reduction in tumor size after induction chemotherapy, radiotherapy, and temozolomide. The successful neoadjuvant therapy makes debulking surgery possible in our patients. With multimodality treatment, our patient survives for more than five years with stable disease.

Neuroblastoma has to be considered a differential diagnosis of neck lump despite its rare incidence in adolescents. Early and accurate histopathology examination has an important role in confirming the diagnosis. Regarding the chemo-resistant profile of neuroblastoma in adolescents, early and multimodality treatments are important to achieve disease control.

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