Risk Factor Analysis of Anxiety Disorder in Third Trimester Pregnant Women

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ABSTRACT

Introduction: Pregnancy is normal for productive women. Pregnancy anxiety is an emotional response related to the concern felt by the mother for the well-being of herself and her fetus during pregnancy, childbirth and future motherhood. The purpose of this study was to determine the relationship between age, education level, occupation, economy, parity, environmental status, and religious spiritual activity on anxiety disorders in third trimester pregnant women in Somba Opu District, Gowa Regency.
Methods: This research is an observational study with a cross-sectional design using quantitative data using a purposive sampling method with the slovin formula and a population of 445 people is obtained to determine the risk factors for anxiety disorders in third trimester pregnant women. The instrument in this study used a questionnaire. The sample used in this study consisted of 136 third trimester pregnant women. Processed data were analyzed according to the Chi Square test p <0.05.
Results: The results showed that there was a significant relationship between the chi-square value between age (0.000), educational level (0.000), occupation (0.021), economic factors (0.000), parity (0.000) and religious spiritual activity (0.010) with the level of anxiety disorders did not show a significant relationship between living environment status and anxiety in third trimester pregnant women (0.514).
Conclusion: There is a relationship between age, education level, occupation, economic factors, parity, and religious spiritual activity with anxiety levels and there is no relationship between living environment status and anxiety in third trimester pregnant women.

Keywords: Female; anxiety; anxiety disorders; pregnancy trimester; risk factors

Introduction

Productive women are closely related to pregnancy. The women will definitely be very happy to know that she is pregnant. However, being pregnant is also closely related to anxiety. This arises because of psychological and physical factors that are worried about the condition of the baby. the changes referred to are not experiencing menstruation, breasts begin to enlarge, abdomen enlarges, enlarges the shape of the uterus, increases body weight, weakens the relaxation of the digestive tract muscles, sensory sensitivity, enlarges extremities and changes in the working system of the organs in the body. [1,2]

The most common psychiatric disorder is anxiety. The National Comorbidity Study reports that 1 in 4 people who carry out the examination meet the diagnostic criteria for at least one anxiety disorder. Women dominate this anxiety (30.5%) compared to men (19.2%).[3]

Emotional worries related to the worries felt by the mother are responded to with excessive anxiety especially about the welfare of themselves and the fetus both during pregnancy, childbirth and the mother's role as a parent.[4]

Mothers often experience anxiety when approaching labor, namely the third or final trimester, how mothers think about pain during childbirth, whether their lives and the lives of their fetuses are safe or not. When the delivery schedule is getting closer, especially during the first pregnancy, it is natural that feelings of anxiety and fear arise, this is something new and can be a meaningful experience.[5]

Anxiety and fear of getting pregnant can cause a storm of contractions to miscarriage and increased blood pressure so that it can be one of the triggering factors for the occurrence and increase in intoxication.[6]

Based on data from the Ministry of Health of the Republic of Indonesia, in 2016 there were 373,000,000 pregnant women in Indonesia, and as many as 107,000,000 pregnant women (28.7%) experienced anxiety in the face of childbirth. There are about 679,765 pregnant women from the entire population in Java, who experience anxiety in the face of childbirth 355,873 people (52.3%).[7]

South Sulawesi Province is one of the provinces with the highest number of maternal and infant deaths in Indonesia. Based on data from the South Sulawesi Health Office, every week two mothers and 16 newborns die in South Sulawesi. In 2017 there were 115 maternal deaths and 817 neonatal deaths. Gowa Regency was recorded as the district with the highest number of maternal death cases at 113 cases, while the largest number of neonatal deaths occurred in Jeneponto Regency with 79 deaths. (Provincial Health Office of South Sulawesi, 2017). Many factors cause high maternal mortality and infant mortality , one of which is the emotional condition of the mother during pregnancy to birth.[8]

The purpose of this study was to determine the relationship between age and level of education, occupation, economy, parity, environmental status, and spiritual activity on anxiety disorders in third trimester pregnant women.

Method

This study was an observational study with a cross sectional approach using quantitative data. The independent variables in this study are age, education, occupation, economic status, parity, environmental status, while the dependent variable is anxiety disorders. The research was conducted in two locations, namely in the Syekh Yusuf Hospital area and the Somba Opu Health Center. In conducting this research there are matters related to research ethics, namely by making a letter of introduction addressed to a party or agency as an application for permission to conduct research with research number 9676/S.01/PTSP/2020

The study population was all third trimester mothers who had ante-natal care at Syekh Yusuf Hospital and the Somba Opu Health Center in July-September 2020, totaling 445 people. The sample used amounted to 136 samples, with the sampling technique using purposive sampling. The sample inclusion criteria were pregnant women with a gestational age of 28-40 weeks, while the sample exclusion criteria were pregnant women who were mentally and physically ill and had a history of chronic disease before and during pregnancy. The data used in this study are primary data and secondary data obtained from the questionnaires made. After the data is collected, then the data is processed in SPSS to see the relationship between the independent and dependent variables using the chi-square hypothesis test with a confidence level of 90% ($\alpha = 0.10$).

Result

Univariate Analysis

Table 1. Distribution of respondents based on the level of anxiety in third trimester mothers in Somba Opu district, Gowa regency in 2020 (n=136)

Characteristic	N (%)
Anxiety levels	
Non Anxiety	13 (9,6)
Anxiety	40 (29,4%)
Moderate Anxiety	48 (35,3%)
Severe Anxiety	34 (25%)
Very Severe Anxiety	1 (0,7%)

Source: Primary Data

Table 1 above shows the distribution of the number and anxiety levels of the respondents. Moderate level was 48 respondents (35.3%) followed by mild anxiety by 40 respondents (29.4%) followed by severe anxiety by 34 respondents (25%). While not anxious as many as 13 respondents (9.6%) and 1 person (0.8%) with very severe levels of anxiety.

Bivariate Analysis

Table 2. The relationship between age and anxiety levels of third trimester pregnant women

		Young Age <20th)	Age Productive Age (20-35th)	Old Age (>35th)	Total	*Chi-Square (p-value)*
Anxiety Disorder	Non Anxiety	0	21	0	21	0.000
	Anxiety	0	33	3	36	
	Moderate Anxiety	2	39	3	44	
	Severe Anxiety	15	15	4	34	
	Very Severe Anxiety	0	1	0	1	
Total		17	109	10	136	

Source: Primary Data

Table 2 explained a chi-square of 0.000 was obtained, which means there is a significant correlation between age and the occurrence of anxiety disorder in third trimester pregnant.

Table 3. The relationship between education and anxiety level in third trimester pregnant

		Level of Education					Total	*Chi-Square (p-value)*
		Not School	Graduated from elementary school	Graduated from junior high school	Graduated from high school	Bachelor		
Anxiety Disorder	Non Anxiety	0	0	0	0	11	11	0.000
	Anxiety	0	0	0	22	16	38	
	Moderate Anxiety	0	2	4	35	10	51	
	Severe Anxiety	2	7	7	15	4	35	
	Very Severe Anxiety	0	1	0	0	0	1	
Total		2	10	11	72	41	136	

Source: Primary Data

The results of this study obtained a chi-square of 0.000 which means there is a significant correlation between the relationship between education level and the occurrence of anxiety disorder in third trimester pregnant women.

Table 4. The relationship between work and anxiety levels in third trimester pregnant women

		Age Factor					Total	*Chi-Square (p-value)*
		Unemployment	Merchant	Private employees	Government employees	Other		
	Non Anxiety	4	1	7	3	0	15	0.021
	Anxiety	18	4	8	5	0	35	
Anxiety	Moderate Anxiety	37	7	4	2	1	51	
Disorder	Severe Anxiety	27	3	4	0	0	34	
	Very Severe Anxiety	1	0	0	0	0	1	
Total		87	15	23	10	1	136	

Source: Primary Data

Table 4 above shows that in the highest group of respondents who did not work or were housewives, who experienced moderate anxiety as many as 37 people (27.2%). The results of this study obtained a chi-square of 0.021 which means there is a significant correlation between the relationship between the work of pregnant women and the occurrence of anxiety disorder in third trimester pregnant women.

Table 5. The relationship between economic factors and anxiety levels in pregnant women's third trimester

		Economics Factors		Total	*Chi-Square (p-value)*
		Low economy	High economy		
	Non Anxiety	3	12	15	0.000
	Anxiety	24	15	39	
Anxiety	Moderate Anxiety	40	9	49	
Disorder	Severe Anxiety	31	1	32	
	Very Severe Anxiety	1	0	1	
Total		99	37	136	

Source: Primary Data

Table 5 explained that in the group of respondents who have a low economic level (have a total income below Rp.3,103,800), who have a severe anxiety level as many as 31 people (22.8%), who have moderate anxiety as many as 40 people (29.4%), who have mild anxiety as many as 24 people (17.6%). The results means there is a significant correlation between the relationship of economic factors with the occurrence of anxiety disorder in third trimester pregnant women.

Table 6. The relationship between maternal parity and anxiety levels in pregnant women's third trimester

		Parity Factors					Total	*Chi-Square (p-value)*
		hasn't given birth yet/first pregnant	1 child	2 child	3 child	4 child		
Anxiety Disorder	Non Anxiety	0	1	10	3	0	14	0.000
	Anxiety	3	16	17	2	0	38	
	Moderate Anxiety	20	13	12	6	2	53	
	Severe Anxiety	20	7	1	1	1	30	
	Very Severe Anxiety	0	1	0	0	0	1	
Total		43	38	40	12	3	136	

Source: Primary Data

Table 6 above shows that in the highest group of respondents who had a first pregnancy (primogravida), who experienced severe anxiety as many as 20 people (14.7%), who had moderate anxiety levels as many as 20 people (14.7%). The results of this study obtained a chi-square of 0.000 which means there is a meaningful correlation between the relationship of parity with the occurrence of anxiety disorder in third trimester pregnant women.

Table 7. The relationship between environmental status and anxiety levels in third trimester pregnant women

		Risk Factor		Total	*Chi-Square (p-value)*
		Living with husband	Living with family		
Anxiety Disorder	Non Anxiety	7	7	14	0,514
	Anxiety	25	13	38	
	Moderate Anxiety	30	20	50	
	Severe Anxiety	17	17	34	
Total		79	57	136	

Source: Primary Data

Table 7 explained the results obtained a chi-square of 0.514 there is no significant correlation between the relationship between environmental status and the occurrence of anxiety disorder in third trimester pregnant women.

Table 8. The relationship between religious spiritual activity and anxiety levels in third trimester pregnant women

		Good Spiritual	Risk Factor Spiritual Enough	Less Spiritual	Total	*Chi-Square (p-value)*
Anxiety Disorder	Non Anxiety	7	6	0	13	0.010
	Anxiety	13	23	0	36	
	Moderate Anxiety	12	41	0	53	
	Severe Anxiety	1	31	1	33	
	Very Severe Anxiety	0	1	0	1	
Total		33	102	1	136	

Source: Primary Data

Table 8 explained the results of this study obtained a chi-square of 0.010 which means there is a significant correlation between the relationship between religious spiritual activities and the occurrence of anxiety disorder in third trimester pregnant women.

Discussion

Based on the young age group (<20 years), totaling 17 people (12.5%), the majority had a severe level of anxiety of 15 people (11%). Whereas in the third trimester pregnant women in the moderate age group (20-35 years) as many as 109 people (80%) experienced moderate anxiety, namely as many as 39 people (28.7%), and in pregnant women in the old age group (> 35 years) The majority of 10 people (7.4%) experienced severe anxiety as many as 4 people (3%). The research results obtained were correlated with research studies, the majority of which were in the young age group (<20 years). According to the researcher Handayani (2017), mothers aged <20 years and ≥ 35 years often experienced feelings of anxiety and fear of giving birth. Pregnancy at that time is included in the category of pregnancy that has a high risk so that abnormal births can occur.[9]

This study is in line with previous studies, namely that of 53 respondents in the third trimester of primigravida pregnant women who had a high level of education (graduates ≥ high school), most of them had a moderate level of anxiety as many as 40 people (75.5%), followed by pregnant women who had a high level of anxiety. mild as many as 7 people (13.2%), while pregnant women who have an education level < high school have a severe level of anxiety.[10]

The results of Heriani's research (2016) at the Tanjung Agung Health Center, Ogan Komering Ulu

Regency, showed that the education of the majority of pregnant women was < SMA, which was low at 74.0% (17 respondents). Low majority results as many as 15 people (50.0%). Pregnant women with low schooling or dropping out of school will depend on the mother's intellectual knowledge of pregnancy information so that ignorance will cause fear to the point of experiencing anxiety.

Pregnant women who have a low level of education will be more likely to experience anxiety due to the lack of information obtained about their pregnancy. Pregnant women with low education are also embarrassed to discuss or ask questions about their pregnancy with friends or neighbors who are pregnant as well or to midwives. And this has an impact on the level of anxiety of pregnant women to increase because of feelings of worry about their pregnancy and childbirth later.[11]

This study is similar to the previous research conducted by Said, 2015, which was obtained from 9 respondents of primigravida pregnant women who had more jobs did not experience anxiety, namely as many as 6 people (66.7%), while from 31 respondents of primigravida pregnant women who did not work, more experienced anxiety as many as 16 people (51.6%).[11]

Working mothers will automatically be busy so that their activities take up a lot of time. However, the positive thing is that pregnant women can interact more with the community while working so that they can increase their knowledge about their pregnancy, and also increase their salary and additional income when working diligently..[12]

Based on the results of research on third trimester pregnant women in pregnant women who have low economic status, with income lower than the Minimum Wage moderate anxiety which is as much as 40 thousand (29.4%). In pregnant women who have high economic status as many as 37 people (27.2%) and most experience mild anxiety as many as 15 people (11%).

This research is in line with the research of Said, Kanine and Bidjuni (2015) obtained from 23 pregnant women respondents. Most primigravidas with high economic status do not experience anxiety as many as 20 people (87%). Meanwhile, out of 17 primigravida pregnant women respondents, anxiety would increase as many as 16 people (94.1%).

The results of the research are in line with those conducted by Deswita (2019) that reading the Koran is definitely a cure for all diseases including anxiety, this has been proven in previous research conducted on third trimester pregnant women in the face of labour. Murotal therapy can have the effect of reducing anxiety[13]

According to Al Kaheel (2018) said that Al-Quran therapy has an effect in the form of changes that indicate relaxation or a decrease in tension in the nervous muscles. This therapy is thought to work optimally on the brain, which will stimulate the brain namely neuropeptides, which will provide feedback in the form of pleasure or comfort to someone. [14,15]

Conclusion

Based on the results of the research conducted, there is a risk factor relationship between age, education level, occupation, economic factors, parity, religion, spiritual activities with the anxiety level of third trimester pregnant women. However, there is no significant relationship between environmental status and anxiety in pregnant women.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no conflict funding sources

Acknowledgments

There is no acknowledgment

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Association of Nutritional Intake and Toddler Development

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ABSTRACT

Introduction: This study explores the impact of nutritional intake on the growth and development of children, particularly in terms of brain development during the toddler phase. The objective was to establish a link between nutritional intake and children's development.

Methods: This research employs a quantitative approach, utilizing an analytical survey design with a cross-sectional methodology. The research tools consisted of a developmental pre-screening questionnaire and a Food Frequency Questionnaire (FFQ). The sample included 74 children aged 1 to 3 years, who were attendees of the Bulukunyi Health Center in Takalar Regency. The data analysis was conducted using the Chi Square test, with statistical significance set at $p < 0.05$.

Results: The study unveiled noteworthy correlations between protein intake ($p = 0.013$), vitamin A ($p = 0.019$), and vitamin C ($p = 0.011$) and the growth and development of children.

Conclusion: This research establishes a positive connection between protein intake, as well as the intake of vitamin C and vitamin A, and the development of children during the toddler phase.

Keywords: Nutrition intake; child development; toddler

Introduction

The quality of the nation's next generation depends on the quality of children's growth and development, especially at the age of toddler (1 - 3) years, when children's brains are in very significant development. Families must make maximum efforts so that their children's growth and development occur optimally; this is to avoid abnormal, doubtful or deviant growth and development. Abnormal growth and development must be detected (found) early, especially before children are 3 years old so that intervention efforts can be made (repaired) immediately. If it is detected too late, it will be too late to take action, making it difficult to correct the abnormality. Childhood is considered as a very important phase of life because it will determine the quality of one's health, well-being, learning ability and behavior in the future; and the future of society depends on the ability of children to achieve optimal growth and development.[2]

According to data millions of children who always get problems in the developmental period. WHO data for 2021 shows that the number of stunting cases in the world has reached 22% or as many as 149.2 million cases in 2020.[3][4] In 2020 UNICEF stated that stunting reflects chronic malnutrition and can have long-term impacts, one of which is a decrease in the development of cognitive and mental abilities.[5] The results of a study related to Indonesia's nutritional status in 2022 show that South Sulawesi Province is included in the list of the top 10 provinces with the highest number of stunted toddlers with a total percentage of 27.2%[6] and the number of toddlers with malnutrition reaches more than 41,000 children.[7]

Based on the problems above, this study aims to see the correlation between nutritional intake and the development of children at the age of toddlers.

Methods

This is a cross-sectional study that evaluated nutritional intake and toddler growth and development. The variables that were researched in this study were nutritional intake and children's growth and development. This research was conducted at the Bulukunyi Health Center, Takalar Regency, in January 2021. The population who became the object of this study were toddlers at the Bulukunyi Health Center. The samples in this study were toddlers using the purposive sampling research method, where samples were taken according to participants who had inclusion and exclusion criteria. Inclusion criteria: [1] toddlers with mothers who are willing to fill out the questionnaire, [2] children aged 1-3 years who live in the study area, and [3] children who were healthy at the time of the study; while on the other hand the exclusion criteria are toddlers who suffer from congenital defects and mothers of children who have a mental disorder and unable to communicate. The number of case samples that fit the inclusion and exclusion criteria was 74 people. Primary data for this research comprised toddler nutritional intake information, which participants provided by completing the food frequency questionnaire (FFQ) obtained from the Ministry of Health and also used

by Nurmalita Sari (2015) in her research. Children's developmental data, on the other hand, was sourced from the KPSP. Following data collection, the information was subjected to processing using the SPSS software. Initially, univariate analysis was applied to establish the frequency distribution of the variables under examination. Subsequently, a bivariate analysis was performed utilizing the Pearson Chi-square test to ascertain the potential correlation between nutritional intake and children's development.

Result

Univariate analysis

Table 1

Characteristics of respondents in Bulukunyi Health Center

Respondent Characteristic	N	%
Age of Toddler		
1-2 year	23	31,1
2-3 year	51	68,9
Work		
Government employees/Army/Policy	-	-
Trader	2	2,7
Farmer	13	17,5
Housewife	59	79,7
Education		
No school	3	4,05
Elementary school	20	27,02
Junior High School	10	13,5
Senior High School	36	48,6
University	5	6,75
Total	74	100

Primary Data, 2021

Based on Table 1 above, it can be seen that the majority of respondents have children aged 2-3 years, namely as many as 51 people (68.9%), respondents with housewife jobs are 59 people (79.7%) and respondents with high school education are 36 people (48.6%).

Age of Child

In this study, the distribution of children was carried out based on age grouping categories which can be seen in table 1. The results showed that 31.1% of children were aged 1-2 years and 68.9% of children aged between 2-3 years.

Table 2

Distribution of case samples by age group (n = 74)

Age	Amount	Percentage (%)
1-2 Years	23	31.1

>2-3 Years	51	68.9
Total	74	100

Primary Data, 2021

Protein Nutrition Intake

Sample distribution based on protein nutritional intake can be seen in table 2. The results in this study showed that the consumption of protein nutrition by toddlers who are in the less category was 2.7%, in the good category was 24.3%, and in the over category was 73%.

Table 3

Distribution of case samples based on consumption of protein nutrient intake (n = 74)

Protein	Amount	Percentage (%)
Less	2	2.7
Good	18	24.3
Over	54	73
Total	74	100

Primary Data, 2021

Vitamin C Nutritional Intake

Sample distribution based on nutritional intake of vitamin C can be seen in table 3. The results in this study showed that the consumption of vitamin C nutritional intake was in the less category, amounting to 44.6%; in the good category, amounting to 0%; and in the over category, amounting to 55.4%

Table 4
Distribution of case samples based on consumption of vitamin c nutritional intake (n = 74)

Vitamin C	Amount	Percentage (%)
Less	33	44.6
Good	0	0
Over	41	55.4
Total	74	100

Primary Data, 2021

Vitamin A Nutritional Intake

Sample distribution based on nutritional intake of vitamin A can be seen in table 4. The results of this study showed that the consumption of vitamin A in the less category was 48.6%, in the good category was 0%, and in the more category was 51.4%.

Table 5

Distribution of case-based samples consumption of vitamin a nutritional intake (n=74)

Vitamin A	Amount	Percentage (%)
Less	36	48.6
Good	0	0
Over	38	51.4
Total	74	100

Primary Data, 2021

Children's development

Sample distribution based on children's development can be seen in table 5. The results of this study showed that the development of children in the abnormal category was 16.2%, in the doubtful category was 6.8% and in the Normal category was 77%.

Table 6

Distribution of case samples based on child development (n=74)

Child development	Amount	Percentage (%)
Abnormal	12	16.2
Doubtful	5	6.8
Normal	57	77.0
Total	74	100

Primary Data, 2021

Bivariate Analysis

Correlation between Protein Nutrition Intake and Child Development.

The correlation between protein nutritional intake and children's development can be seen in table 6.

Table 7

Correlation of protein nutrition intake with child development

		KPSP								*P – value*
		Abnormal		Doubtful		Normal		Total		
		N	%	N	%	N	%	N	%	
Protein	Less	7	38,9	0	0	11	61,1	18	100	0,013
	Good	1	50	0	0	1	50	2	100	
	Over	4	7,4	5	9,3	45	83,3	54	100	
Total		12	16,2	5	6,8	57	77	74	100	

The findings demonstrated a link between protein consumption among young children and their KPSP scores. The Chi square statistical analysis yielded a p-value of 0.0131, surpassing the alpha value of 0.05. Therefore, it can be deduced that a notable and favorable association exists between protein intake and child development.

Correlation between Vitamin A Intake and Child Development.

The Association between vitamin A consumption and the development of children can be seen in table 7.

Table 8

Correlation of vitaminA intake with child development

		KPSP								*P – Value*
		Abnormal		Doubtful		Normal		Total		
		N	%	N	%	N	%	N	%	
Vitamin A	Less	10	27,8	1	2,8	25	69,4	36	100	0,019
	Good	-	-	-	-	-	-	-	-	
	Over	2	5,3	4	10,5	32	84,2	38	100	
Total		12	16,2	5	6,8	57	77	74	100	

The analysis outcomes concerning the connection between vitamin A consumption in young children and KPSP indicated that the Chi square statistical test produced a p-value of 0.019, exceeding the alpha threshold of 0.05. Consequently, it can be inferred that a notable correlation exists between vitamin A intake and children's development (KPSP).

Correlation between Vitamin C Intake and Child Development

The correlation between vitamin C intake and child development can be seen in table 8.

Table 9

Correlation between vitamin C intake with child development

		KPSP								P - value
		Abnormal		Doubtful		Normal		Tota I		
		N	%	N	%	N	%	N	%	
Vitamin C	Less	9	27,3	4	12,1	20	60,6	33	100	0,011
	Good	-	-	-	-	-	-	-	-	
	Over	3	7,3	1	2,4	37	90,2	41	100	
Total		12	16,2	5	6,8	57	77	74	100	

The analysis outcomes aboutthe relationship between vitamin C consumption in young children and KPSP demonstrated that the Chi-Square statistical test yielded a p-value of 0.011, which falls below the alpha threshold of 0.05. Hence, it can be deduced that a significant correlation exists between vitamin C intake and children's development.

Discussion

Relationship between protein intake and child development

Based on this research, it can be seen that most children are at the toddler have more protein intake which is equal to 73%. Obtained more protein in older children toddler because the habit of the majority of children in this study liked to eat Moringa leaf vegetables. Based on this study, the majority of mothers in the Bulukunyi Health Center work area often make their children moringa leaf vegetables, this is in line with research that the nutritional content of 2-10 moringa leaf stalks contains 28.25% protein. [8]

The research results are relation to protein intake with developments old age toddler with the results of the test analysis who squares- P-value 0.013. This research is appropriate with Nurul's research (2018) there is a relationship between energy intake and protein intake with gross motor development with each *pvaIue* 0.022 and 0.001. [4][9]

Protein is composed of amino acids, namely essential and non-essential. The amino acid tyrosine is a type of amino acid related to the mechanism of motor movement where tyrosine is a constituent of the neurotransmitter dopamine which plays a role in transmitting impulses from one nerve to another. [4][10]

Other research that supports the relationship between protein intake and child development is research from (Setiawan, 2017) [11] which states that a lack of protein intake affects cognitive abilities, cognitive abilities are brain activities that occur in order to gain knowledge or information. The process of cognitive ability is the occurrence of very active communication between brain cells. Communication between one brain cell and another brain cell occurs through the delivery of messages by a neurotransmitter. The neurotransmitter is a chemical compound consisting of amino acids, namely protein building monomers (amino acid polymers). Hundreds of neurotransmitters are produced in the brain. The production of neurotransmitters requires protein which must be obtained from food intake.[12][13]

Relationship between vitamin A intake and child development

Based on the research, it can be seen that most children at toddler age have more vitamin A intake, which is equal to 51.4%. *Chi-Square P-Vaiue* 0.019. Obtained more vitamin A in children aged toddlers because the majority of children there like to eat kelor leaf vegetables. Based on this research, the majority of mothers in the working area of the Bulukunyi Health Center often make their children Moringa leaf vegetables and the nutritional content of Moringa leaves for every 2 grams of Moringa leaves contains 600 IU of vitamin A.

This study aligns with the findings of (Hapzah 2016), indicating a connection between vitamin A and nutritional status. This is due to the involvement of vitamin A in protein synthesis, upkeep of typical epithelial structure, and the growth of bones.[13][14]

Relationship between vitamin C intake and child development

Based on research, it can be seen that most children at toddler age have more vitamin C intake, namely 55.4%. The results of this study found that there was a relationship between vitamin C intake and the development of toddler aged children with the results of the test analysis *Chi-Square P-vaiue* 0.011. Obtained more vitamin C in older children toddler because the majority of children there like to eat Moringa leaf vegetables. Based on this research, the majority of mothers in the working area of the Bulukunyi Health Center often make their children Moringa leaf vegetables, for the nutritional content of Moringa leaves, every 2 grams of Moringa leaves contain 11 milligrams of vitamin C.[13][15]

Conclusion

Based on result of research about intake relationship nutrition for development old age *toddler* in the BuIukunyi Health Center, TakaIar Regency, it can be concluded that **i**ntake protein, vitamin A, and vitamin C has a significant relationship with child development.

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Sensitivity Molecular Detection for Salmonella *Enterica Serovars Typhi*

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ABSTRACT

Introduction: Salmonella infections contribute significantly to gastroenteritis cases, with the National Salmonella Reference Laboratory reporting 500 isolates in 2022. However, traditional culture-based methods for detecting Salmonella in samples can take 4 to 7 days to confirm a positive result, which poses health risks due to delayed detection. Given these health risks, swift and accurate detection methods are essential to minimize both false-positive and false-negative outcomes.
Methods: The qRT-PCR procedure involved the design of primers and probes targeting the same genes as the mPCR assay. These primer sets were reconfigured to generate smaller amplicons suitable for qRT-PCR systems
Results: qRT-PCR process, TaqMan probes were meticulously designed for specific target genes: FAM dye was employed to detect STM2745, Cy5 dye was used for STM4492, and Rox dye was utilized to detect. A standard curve was constructed using Typhimurium LT2 genomic DNA. Each sample underwent duplicate analysis, and Rotor-Gene software was employed to assign threshold values for each channel
Conclusion: The effectiveness of our qPCR assay for the detection of Salmonella across a diverse array of matrices. Notably, our results unveiled distinct limits of detection for Salmonella in various samples. Specifically, a parallel vein, the deployment of a PCR assay, leveraging an immunomagnetic separation technique for DNA extraction, was studied by another group. While subsequent analysis of Salmonella detected via our assay may necessitate the full ISO SMT method for live culture isolation, this supplementary step can be seamlessly conducted alongside qRT-PCR.

Keywords: Sensitive molecular; salmonella; *detection salmonella*

Introduction

Salmonellosis stands as a prevalent infectious foodborne disease worldwide, affecting both animals and humans. *Salmonella enterica*, a bacterium within the Salmonella genus, is the primary culprit behind a broad spectrum of illnesses, ranging from gastroenteritis to severe, life-threatening enteric fever. Each year, the United States records an estimated 1 million cases of salmonellosis among humans. *S. enterica* ranked as the second most common cause of zoonotic infections among humans within the European Union in 2022, with 900 confirmed cases of salmonellosis reporter.[1]

Salmonella infections contribute significantly to gastroenteritis cases, with the National Salmonella Reference Laboratory reporting 500 isolates in 2022. However, traditional culture-based methods for detecting Salmonella in samples can take 4 to 7 days to confirm a positive result, which poses health risks due to delayed detection. Given these health risks, swift and accurate detection methods are essential to minimize both false-positive and false-negative outcomes. Salmonella, a gram-negative bacterium within the Enterobacteriaceae family, demonstrates remarkable hardiness, surviving for several weeks in dry environments and months in water.[2] Although most serotypes of Salmonella cause relatively mild gastroenteritis, some, particularly those transmitted from animals to humans, can lead to severe, life-threatening conditions. Salmonellosis outbreaks have been widely reported, highlighting the pressing need for improved prevention and control measures globally. Salmonellosis is characterized by fever, abdominal pain, diarrhea, nausea, and sometimes vomiting, after exposure to the bacterium. While most cases resolve without specific treatment, severe dehydration can occur, especially in children and the elderly. Additionally, the disease's transmission often goes unrecognized as a part of known outbreaks, with sporadic cases constituting a significant portion.[3]

Salmonella infections are zoonotic, meaning they can be transmitted between animals and humans. The bacterium is frequently found in the intestines of various animals, particularly poultry, pigs, and cattle. Contaminated foods like eggs and raw meat, as well as improper kitchen hygiene, can lead to human infection. Though many cases resolve on their own, individuals with weakened immune systems, infants, and older adults are at a higher risk of complications. Adequate hygiene, proper cooking, and safe handling of raw foods can help prevent the spread of this disease.[4]

Methods

A total of 150 bacterial isolates were utilized to validate the techniques formulated during this investigation. To assess the specificity of potential serovar regions identified through in silico genome comparisons, two reference collections were employed: Salmonella reference collection A, comprising 50 isolates from serovars within the *S. enterica* Typhimurium complex, and Salmonella reference collection

B, composed of 50 strains representing 50 serovars of *S. enterica*.[5] These collections encompass a diverse range of strains from various geographical origins. Additionally, 50 recent clinical and environmental isolates from Ireland were examined, covering 20 distinct serovars. As part of this study, three National Collection Type Culture (NCTC) strains, including *Escherichia coli* NCTC 9009, Listeria monocytogenes NCTC 11994, and *Staphylococcus aureus* NCTC 6571, were included as negative controls. DNA extraction from each strain was conducted using the Gnome DNA isolation kit (BIO 101, Inc., La Jolla, CA) and/or the Promega (Madison, WI) Wizard genomic DNA purification kit, following the manufacturer's instructions. The objective was to evaluate the developed techniques and investigate potential serovar-specific regions through comparisons of in silico genomes.[6]

The qRT-PCR procedure involved the design of primers and probes targeting the same genes as the mPCR assay. These primer sets were reconfigured to generate smaller amplicons suitable for qRT-PCR systems.[7] The design of sequence-specific primers and TaqMan probes was facilitated by utilizing Primer3 software. The choice of dyes, including FAM, Cy5, and ROX, along with the quenchers BHQ1, BHQ2, and BHQ3, were tailored for compatibility with the Rotor-Gene 6000 system. For qRT-PCR execution, the QuantiTect multiplex PCR NoRox kit was employed, adhering to the manufacturer's guidelines from Qiagen. This approach aimed to ensure optimal primer and probe design for qRT-PCR analysis, facilitating the generation of meaningful results.[8]

Result

qRT-PCR process, TaqMan probes were meticulously designed for specific target genes: FAM dye was employed to detect STM2745, Cy5 dye was used for STM4492, and Rox dye was utilized to detect. A standard curve was constructed using Typhimurium LT2 genomic DNA. Each sample underwent duplicate analysis, and Rotor-Gene software were employed to assign threshold values for each channel. The study examined DNA samples from various common Salmonella serovars. The correlation coefficient was calculated to compare observed data points to the expected standard curve points. A higher R^2 value approaching 1 indicated a better fit of observed data to the standard curve. The obtained R^2 values from the mPCR reaction were all above 0.99, denoting a high level of accuracy. The slope of the standard curve, directly linked to the average amplification efficiency, allowed for calculation of PCR efficiency. Slope values for this qRT-PCR reaction ranged from 23.32 to 23.53. Additionally, the number of qRT-PCR cycles required to detect control strains was determined, yielding cycle threshold (Ct) values ranging from 13.41 to 18.12.

Both conventional mPCR and qRT-PCR assays were carried out at the preenrichment (BPW) and selective enrichment (RVS) stages. The validation of the mPCR assay was conducted using ground raw turkey samples containing S. enterica Heidelberg, Dublin, and Enteritidis cells, and various concentrations

of Typhimurium were also utilized. The initial seeding levels for the meat samples were as follows: 6.1 x 10^8 S. enterica Typhimurium LT2/ml, 5.6 x 10^9 S. enterica Heidelberg (RL9)/ml, 7.5 x 10^8 S. enterica Dublin (CCC8)/ml, and 8.8 x 10^8 S. enterica Enteritidis (UCG1)/ml. This comprehensive approach allowed for effective assessment of the qRT-PCR reaction, highlighting its accuracy and applicability in detecting Salmonella strains across different stages of analysis.
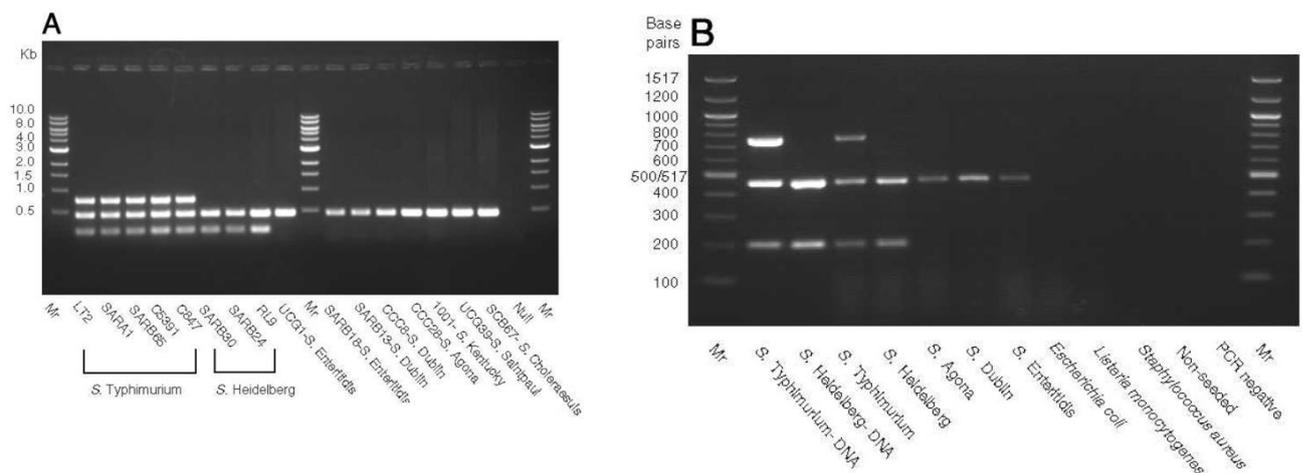
Figure 1 qPCR assays. (A) qPCR assay of a representative panel of Salmonella isolates. Typhimurium strains yielded three bands, Heidelberg isolates yielded the expected two bands, and all Salmonella serovars yielded the expected 461-bp band. (B) qPCR assay of food matrices seeded with Salmonella serovars Dublin, Agona, and Enteritidis, Escherichia coli, Listeria monocytogenes, and Staphylococcus aureus. DNA from Salmonella enterica Typhimurium LT2 and Heidelberg were used as positive controls yielded the expected three PCR bands and two PCR bands, respectively.

Discussion

We assessed the effectiveness of our qPCR assay in detecting Salmonella across various matrices. Our findings revealed distinct limits of detection for Salmonella in different samples: for cheese, raw turkey, and cooked turkey, the limits were 250 CFU/ml of selective enrichment, respectively. An PCR assay using an immunomagnetic separation technique for DNA extraction. Their investigation highlighted the inhibitory effect of food debris present in enrichment broths on PCR.[9]

Intriguingly, they discovered that high-fat-content samples like soft cheese displayed higher detection limits compared to lower-fat-containing foods such as eggs. For instance, the detection limits were 1.5 x 10^3 CFU/25 g of cheese sample and 1 to 5 CFU/25 g of egg sample. In contrast, our research demonstrated a higher sensitivity for detecting Salmonella in high-fat-content foods like grated cheese compared to raw ground turkey meat. The matrix that exhibited the most detrimental impact on sensitivity was raw turkey meat. This reduced detection limit could be attributed to the presence of inhibitory substances or competing microbiota in the matrix.[10] In the realm of PCR assays, TaqMan PCR assays have been created for various

common gene targets to detect Salmonella, such as the stn gene, the ttrRSBCA locus, and the invA gene. Within our study, innovative qRT-PCR targets were devised for identifying Salmonella and differentiating between S. enterica Typhimurium and Heidelberg. Impressively, this differentiation could be achieved with a detection limit of 6.0 x 10^1 CFU/ml from RVS broth within 48 hours.[11]

This speed far surpasses the ISO SMT method, which typically takes 4 to 7 days to complete. While further analysis of Salmonella detected via this assay would necessitate the full ISO SMT method for live culture isolation, this additional step can be concurrently conducted with qRT-PCR–negative samples being disregarded. This streamlined process leads to significant time and labor savings in research.[12]

We employed a meticulous approach to designing a multifaceted mPCR assay for the detection and differentiation of Salmonella. Our assay hinged on three distinct primer pairs: the first targeting an inner membrane protein, the second focusing on another inner membrane protein identified, the third primer pair designed to pinpoint the oriC locus present across all Salmonella strains. By leveraging these primers, we were able to specifically identify and differentiate S. enterica Typhimurium and Heidelberg. Rigorous validation processes substantiated the sensitivity and specificity of our assay.[13]

Our investigation extended further to demonstrate the specificity of our mPCR assay across a range of sample types, including artificially spiked incurred samples, broth media, Cheddar cheese, and raw and cooked ground turkey meat. We conducted these tests on samples seeded with various Salmonella serovars (Dublin, Agona, and Enteritidis) as well as other foodborne pathogens like E. coli, L. monocytogenes, and S. aureus.[14] The outcomes of these tests were definitive, with the presence of Salmonella-specific amplicons observed in all screened Salmonella strains. In contrast, non-Salmonella strains yielded no such amplicons.[15]

Conclusion

The effectiveness of our qPCR assay for the detection of Salmonella across a diverse array of matrices. Notably, our results unveiled distinct limits of detection for Salmonella in various samples. Specifically, a parallel vein, the deployment of a PCR assay, leveraging an immune-magnetic separation technique for DNA extraction, was studied by another group. While subsequent analysis of Salmonella detected via our assay may necessitate the full ISO SMT method for live culture isolation, this supplementary step can be seamlessly conducted alongside qRT-PCR. This streamlined approach contributes to significant time and labor savings in research. Furthermore, our meticulous approach extended to the design of a multifaceted mPCR assay. This assay hinged on three distinct primer pairs

targeting specific elements: an inner membrane protein, a different inner membrane protein, and the oriC locus present across all Salmonella strains. Our utilization of these primers enabled the specific identification and differentiation of S. *enterica Typhimurium* and Heidelberg. This differentiation was fortified by rigorous validation, underscoring the sensitivity and specificity of our assay.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no funding sources

Acknowledgments

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REVIEW ARTICLE   **Open Access**

Polycythemia Vera: A Malignancy in Hematology: Review Article

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ABSTRACT

Introduction: Myeloid neoplasm is a condition in which myeloid cells can undergo excessive clonal proliferation. One classification of the disease is polycythemia vera. Polycythemia Vera (PV) is a condition where there is an increase in the number of red blood cells reaching 125% of the calculation based on body mass and sex.
Content: This journal discusses polycythemia vera including the definition, epidemiology, etiopathogenesis, clinical manifestations, diagnosis, management and complications.
Result: Characteristics of diseases in obese patients at RSUD Dr. H. Chasan Boesoirie Ternate in 2019 were found to be 20-60 years 75 people (80%), women 69 people (72.6%), work as housewives 54 people (56.8%), the level of high school education was 36 people (37.9%), obesity I 68 people (71.6%), and the type of type 2 diabetes mellitus 46 people (48.4%).
Conclusion: PV is caused by mutations in the JAK2 gene. PV disease diagnosis based on the results of the history, physical examination and supporting examinations in the form of laboratory tests. PV disease can be managed with phlebotomy, administration of aspirin, and cytoreductive drugs. Patients with PV can survive more than 10 years if treated quickly and appropriately

Keywords: Neoplasm; myeloproliferative; polycythemia vera

Introduction

An increase in the number of circulating red blood cells that persists for more than two months is considered polycythemia[1,2]. The syllable polycythemia when interpreted in Greek means poly (many), cyt (cells) and hemia (blood) [1]. The number of cases of polycythemia in general is quite large throughout the world.

In general, the classification of polycythemia is divided into two, namely polycythemia vera and secondary polycythemia. It is important to distinguish between the two diseases because often patients present with cardiovascular disease which is one of the earliest features of polycythemia, especially polycythemia vera[2]. In addition to the sake of diagnosis, the importance of distinguishing the two diseases is to determine the appropriate treatment given to patients with these diseases to reduce morbidity and mortality due to these diseases[2]. In this literature review, we will discuss about polycythemia from definition to proper management in dealing with polycythemia cases.

Definition

Polycythemia comes from the Greek words *poly* meaning many, *cyt* meaning cells, and *hemia* meaning blood. So polycythemia is a condition where there is an increase in the number of red blood cells reaching 125% of the calculation based on body mass and sex[1,2]. Polycythemia is also known as erythrocytosis which indicates a persistent increase in hematocrit levels > 2 months[3].

In general, polycythemia can be grouped into primary polycythemia or polycythemia vera and secondary polycythemia. Primary polycythemia or vera occurs due to excessive intrinsic activity in the bone marrow progressively and chronically because most of the erythrocyte population comes from an abnormal stem cell clone while secondary polycythemia occurs due to abnormalities in the bone marrow through increased erythropoietin due to certain factors[2].

Epidemiology

Globally, the incidence of primary polycythemia/vera (PV) is 1.9 per 100,000 people [3]. The incidences of PV are common in males and dominated by the age of 40-60 years. The annual incidence rate of PV is 2.3 per 100.000 population. The survival rate of PV without treatment is only 1.5 – 3 years while with treatment it can reach 10 years [1].

Etiopathogenesis

PV is a chronic myeloproliferation neoplasm with a negative Philadelphia chromosome that causes a clonal disorder of myeloproliferation in the spinal cord[4,5]. Myeloid cell proliferation is being replaced by an abnormal monoclonal proliferation process causing overproduction of red blood cell, platelet in essential thrombocytosis, and spinal cord fibrosis in primary myelofibrosis[6]. In 2005, researchers discovered a somatic mutation in the Janus kinase 2 (JAK2) gene. The JAK2 gene provides instructions for making proteins that play a role in cell proliferation[7]. This protein has an important role in controlling the production of erythrocytes, leukocytes, and platelets in hematopoietic stem cells in the bone marrow[8]. The JAK2 gene mutation most commonly associated with myeloproliferative neoplasms is located at exon 14 of JAK2. This mutation in exon 14 is called JAK2V617F[9]. JAK2V617F can be found in more than 90% of PV, as well as 50-60% in ET and PMF7. A small proportion of PV patients have a JAK2 mutation in exon 12[10]. The JAK2V617F mutation causes genetic instability in gene expression by triggering changes in chromatin structure and by reducing apoptotic responses to DNA damage[11]. The occurrence of mutations in JAK2 causes erythropoietin hypersensitivity which results in increased production of red blood cells[11]. Polycythemia vera naturally tends to progress to myelofibrosis, called post-polycythemia vera myelofibrosis (PPVMF)[12]. This transformation occurs in 25% of PV patients and decreases life expectancy[10]. There are no risk factors for the evolution of PV to PPV-MF. In PPV-MF, an increase in JAK2V617F was found as in PV, and CD34+ cells in peripheral blood[13].
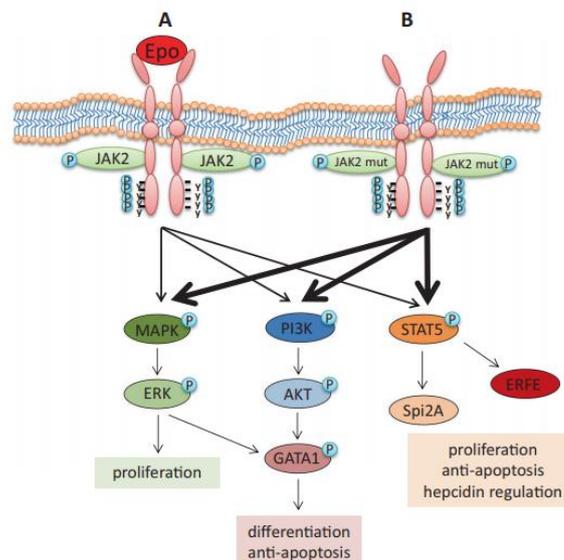

Figure 1. Mediated signaling *JAK2* [7].

Clinical Manifestation

Signs and symptoms of PV are divided into 3 phases, namely:

1.   Early symptoms (*early symptoms*)

The initial symptoms of PV are minimal or even abnormalities are not always found even though it has been known through laboratory tests. The initial symptoms that occur are usually high blood pressure (72%), headache (48%), easy fatigue (47%), ringing in the ears (43%), itching (pruritus) (43%), visual disturbances (3l%), feeling sick. fever in the hands or feet (29%), memory impairment, difficulty breathing (26%), bone pain (26%), also bleeding from the nose, stomach (stomach ulcers) (24%).

2.   Late symptoms*and*complications

As the disease progresses, patients with PV develop*hemorrhage*or thrombosis. Thrombosis is the most common cause of death from PV. Another complication is an increase in uric acid in the blood of about 10%, developing gout and an increased risk of peptic ulcer (10%).

3.   Splenomegaly phase

About 30% of late symptoms progress to the splenomegaly phase. At this stage, bone marrow failure occurs and the patient becomes severely anemic, the need for transfusion increases, the liver and spleen are enlarged[1].

Diagnosis

The initial diagnosis is based on anamnesis, physical examination, and investigation[2].

1.   History

In the history, it is necessary to know a history of tumor or malignancy, cardiovascular and cerebrovascular disorder, a family history of disease associated with myeloproliferative, neoplasms such as polycythemia vera, essential thrombocythemia, or primary myelofibrosis.

2.   Physical Examination

On physical examination can be found splenomegaly and hepatomegaly, ruddy cyanosis (swelling of the mucosa and skin with cyanosis), conjunctiva plethora, and skin plethora (accumulation of fluid and blood in the conjunctiva and mucosa).

3.   Support Inspection

Pemeriksaan pada polisitemia
Pemeriksaan Awal
Pemeriksaan hitung darah lengkap dan apusan darah tepi
Pemeriksaan zat besi/ ferritin
Mutasi JAK2
Konsentrasi EPO serum
Saturasi oksigen dan urinalisis (jika belum diperiksa sebelumnya)
Profil renal dan hepar (jika belum diperiksa sebelumnya)
Pemeriksaan Lanjutan
USG abdomen
Foto toraks
Pemeriksaan polisonografi (sleep test) atau fungsi paru
Aspirasi dan biopsi sumsum tulang
Mutasi JAK2 ekson 12
Pengukuran massa eritrosit
Analisis gen EPO reseptor
Analisis VHL

Figure 2. PV Support Inspection

Erythrocytes

To establish the diagnosis of polycythemia vera during the disease, an elevated erythrocyte mass must be demonstrated. The erythrocyte cell count is >6 million/ml in men and >5.5 million/ml in women, and erythrocyte smears are usually normochromic, normocytic unless iron deficiency is present. Poikilocytosis and anisocytosis suggest a transition to myeloid metaplasia late in the course of the disease.

Granulocytes

Granulocytes increase in number occurs in 2/3 cases of PV, ranging from 12-25 thousand/ml but can be up to 60 thousand/mL. In two-thirds of these cases there is also basophilia.

Platelets

Platelet counts usually range from 450-800 thousand/mL, even >1 million/ml. Often found with abnormal platelet morphology. d. B12 Serum B12 serum can be increased this is found in 35% of cases, and can also be decreased this is found in 30% of cases, and UB12BC levels are increased in >15% of cases of polycythemia vera

Bone Marrow

This examination is not necessary for diagnostics unless there is suspicion of other myeloproliferative diseases such as the presence of blast cells in the leukocyte count. Bone marrow cytology showed an increase in normoblastic cellularity in the form of trilinear hyperplasia of a series of erythrocytes, megakaryocytes, and myelocytes. Meanwhile, from the histopathology of the bone marrow, the presence of a pathological/abnormal morphological form of megakaryocytes and slight fibrosis is a pathognomonic sign of polycythemia vera.

Cytogenetic examination

In polycythemia vera patients who have not received P53 treatment or cytostatic chemotherapy, a karyotype can be found (see etiology). Variations of cytogenetic abnormalities can be found in addition to the above, especially if you have received P53 treatment or previous cytostatic chemotherapy[1].

Table 1. World Health Organization (WHO) Criteria for Diagnosis of Polycythemia Vera

Major Criteria	
Criteria 1	
Hemoglobin	Male: > 16.5 g/dl Female: > 16.0 g/dl
Hematocrit	Male: > 49% Female: > 48%
Red blood cell mass	An increase of 25% above average
Criteria 2	
Bone marrow morphology	Hypercellularity for age with panmyelosis, including prominent erythroid, granulocytic, and megakaryocyte proliferation with pleomorphic and mature megakaryocytes (different sizes)
Criteria 3	
*JAK2 V617F mutation*or	+
JAK2 exon 12 mutation	+
Minor Criteria	
Serum erythropoietin level	Subnormal

Table 2. International Working Group-Myeloproliferative Neoplasms Researchand Treatment (IWG-MRT) criteria for the diagnosis of secondary myelofibrosis

Major Criteria	
Criteria 1	
Documentation of previous diagnosis of polycythemia vera	+
Criteria 2	
Bone marrow morphology	Reticulin fibrosis grade 2/3 (0-3 scale), or reticulin fibrosis grade (on a 0-4 scale)
Minor Criteria	
Anemia* or not meeting requirements for phlebotomy and cytoreduction	There is
Leukoerythroblastosis	There is
Spleen size	Increased splenomegaly, defined as an increase in the size of the splenomegaly by 5 cm (calculated from the left costal arch) or newly palpated splenomegaly
Accompanying symptoms **	Consists of 1 of 3 symptoms

*Defined as hemoglobin value < 12 g/dL for female, and < 13.5 g/dL for male
* Weight loss of 10% for 6 months, cold sweats, and fever of unknown cause (temperature >37.5 C)

Management

Current PV therapy cannot prevent the natural evolution of diseases such as post-PV myelofibrosis, but it can reduce the risk of thromboembolism and bleeding. Initial therapy for PV was phlebotomy and aspirin administration to all patients, both male and female, regardless of risk factor classification. A phlebotomy is performed until the hematocrit is below 45%, and aspirin is given at a dose of 40-100 mg once a day. In low-risk PV patients with microvascular symptoms not controlled with once-daily aspirin, the aspirin dose is increased to twice daily[9].

High-risk patients can be given a cytoreductive drug such as hydroxyurea as a first line with an initial dose of 500 mg twice daily 15 in patients with a history of arterial thrombosis, aspirin is given twice daily. If a history of venous thrombosis is found, systemic anticoagulation should be added. If there is intolerance or resistance to hydroxyurea, second-line drugs should be considered, namely pegylated interferon, busulfan, and ruxolutinib [9]
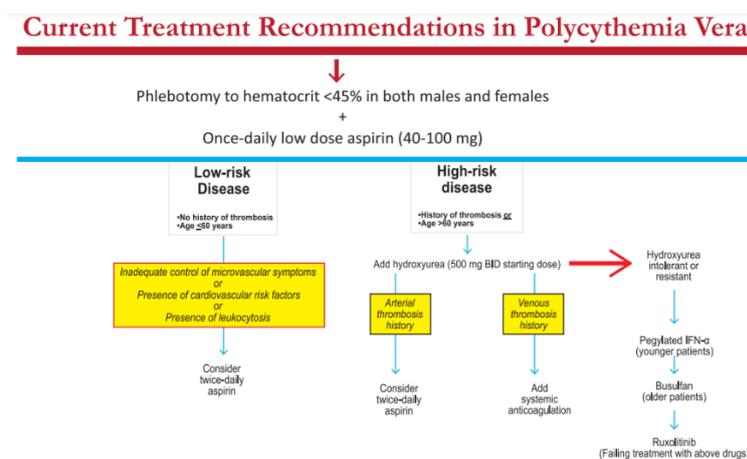

Figure 2. Recommendations for Management of Polycythemia Vera[9]

Complications

PV disease can cause various complications if not treated quickly and appropriately. Several complications that can occur, including thrombosis, bleeding, and transformation into leukemia. Thrombosis is the most frequent complication, which is 34-39%. Mutation *JAK2* causes activation and interaction of leukocytes and platelets that cause inflammation, causing vascular endothelial dysfunction[14].

While Erythrocytosis causes hyperviscosity of blood that triggers thrombosis. The stratification of risk factors for this disease aims to predict the occurrence of thrombotic complications. The risk assessment consisted of two categories: low risk without thrombocytosis (age <60 years without a history of

thrombosis, low risk with high platelets (>1,000 x 109/L). High risk, namely age >60 years with a history of thrombosis. High risk with PV refractory or intolerant to hydroxyurea[14]
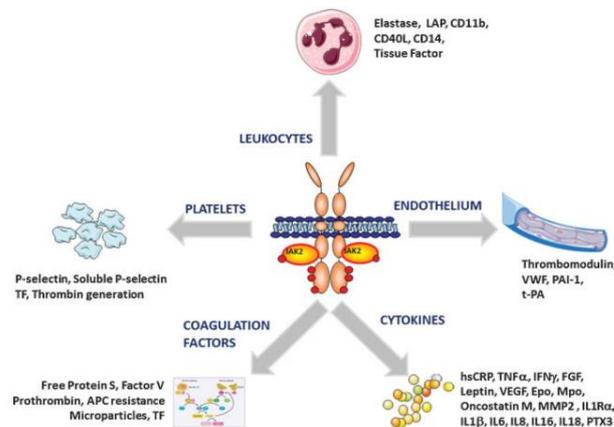
Figure 3: Effect of *JAK2*[14]

Prognosis

In general, PV patients have an average life expectancy of more than ten years in various studies, but it is hoped that the new decade would bring a greater life expectancy supported by the development of new medicines. Thrombosis is the most common cause of morbidity and mortality in cases of polycythemia vera, followed by myelofibrosis and the development of leukemia[15].

Conclusion

Polycythemia vera (PV) is a condition where the red blood cell count increases up to 125% of the calculation based on body mass and sex or a persistent increase in hematocrit > 2 months. The incidence of primary polycythemia/vera (PV) is 1.9 per 100,000 people. The etiology of PV is associated with a mutation in the JAK2 gene.

The diagnosis of PV can be made through history, physical examination, and investigations. There are two criteria that are used as a reference in establishing the diagnosis of PV, namely the WHO criteria and the IWG-MRT criteria. The principle of management of PV is to control the number of erythrocytes with initial therapy in the form of phlebotomy and administration of aspirin. Then individuals with high risk can be given hydroxyurea as the first line. Patients with PV can have a survival rate of more than 10 years if they receive appropriate treatment.

Conflict of Interest

There is no conflict of interest

Funding Sources

Acknowledgment

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REVIEW ARTICLE   **Open Access**

Inspiratory Muscle Training in Chronic Obstructive Pulmonary Disease Patients: A Scoping Review

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ABSTRACT

Introduction: COPD is a leading cause of chronic disease and death globally, with high mortality rates for those hospitalized or requiring mechanical ventilation. Delaying disease progression and improving patient outcomes can reduce healthcare costs and societal impact. Respiratory muscles play a crucial role in COPD, and specific endurance respiratory exercises have been shown to improve muscle fibers and mitochondrial activity, reducing oxidative stress and fatigue. Inspiratory Muscle Training (IMT) is a recommended pulmonary rehabilitation technique that enhances lung capacity and improves exercise performance by altering muscle fiber types and distribution. However, the impact of IMT implemented in COPD remains unclear. This scoping review summarizes the existing studies relating to the potential application of IMT in COPD patients.

Content: A scoping review was performed in PubMed, Academic Search Complete/EBCSCO, and Grey Literature sources, including Google Scholar. IMT studies evaluate interventions for COPD patients that were published in 2018-2023 were included.

Results: We reviewed 644 studies, nine IMT interventions met inclusion criteria and were included in the current study. In the majority of studies, improvements were noted through the implementation of IMT interventions. Several facilitators and barriers were noted during implementation and contributed to the success or failure of the intervention.

Conclusion: Overall, IMT had conflicting effects on a variety of COPD patient outcomes. Numerous studies demonstrated, however, that IMT can improve COPD-related outcomes, such as respiratory muscle function, dyspnea symptoms, quality of life, autonomic function, exercise tolerance, diaphragmatic strength and reduced exertional dyspnea, and balance.

Keywords: Scoping review; inspiratory muscle training; chronic obstructive pulmonary disease

Introduction

COPD is among the primary causes of chronic disease and death worldwide.[1] Annual death rates range from 11 to 50 percent for those who require hospitalization due to a COPD exacerbation, from 5 to 50 percent for those who require mechanical ventilation, and from 37 to 80 percent for those who are readmitted to the hospital due to a previous exacerbation.[2] Health care costs may be reduced and the disease's global and societal effect lessened if actions are taken to delay the progression of the disease and improve patients' prognoses.[3] Individuals with COPD have restricted exercise capacity due to several factors, including breathing, gas exchange, cardiovascular disease[4], and peripheral muscle abnormalities.[5]

Respiratory muscles are responsible for increasing airflow to the lungs by raising the ribs and widening the chest wall, as well as decreasing airway resistance and intrathoracic pressure.[6] It is possible that the activation of respiratory muscles during respiration differs substantially from that of other skeletal muscles. However, the capacity of these two muscle groups to adapt to a variety of situations and functional demands is comparable, culminating in a comparable response to a training stimulus.[6,7] Powers and Criswell (Year?) have discovered that specific endurance respiratory exercise improved the number of fibres and mitochondrial activity in respiratory muscles.[8] The research determined that exercise had a positive effect on oxidative stress and delayed respiratory muscle fatigue.[8] Type I, type IIA, and type IIB fibres are prevalent in respiratory muscles and are also found in peripheral skeletal muscles. Type I, Type IIA, and Type IIB muscle fibers are classifications based on contraction speed, fatigue resistance, energy production, and suitability for different activities. Type I fibers contract slowly, resist fatigue, rely on aerobic energy, and excel in endurance tasks. Type IIA fibers contract moderately, have intermediate fatigue resistance, use aerobic metabolism, and are suitable for mixed endurance-strength activities. Type IIB fibers contract rapidly, fatigue quickly, depend on anaerobic energy, and are well-suited for intense bursts of activity like sprints or weightlifting. The amount and placement of these fibres in the diaphragm muscle, however, differ from those in other peripheral muscles like the quadriceps. The diaphragm has 80% oxidative fibres (types I and IIA), which are fatigue-resistant fibres, while the quadriceps contains just 35-45%.[9]

COPD patients have inspiratory muscle dysfunction, which is followed by dyspnea and impaired exercise capacity.[10,11] As a consequence, pulmonary rehabilitation is recommended as an effective cardiorespiratory therapeutic technique, resulting in increased exercise performance and reduced dyspnea in individuals with varied degrees of disease severity.(12) Inspiratory Muscle Training (IMT) is a pulmonary rehabilitation technique that enhances physical fitness by maximizing lung capacity.[13]

IMT additionally comes with structural alterations in the types and distribution of muscle fibres in the inspiratory muscles. After five weeks of IMT, the number of type I fibres and the size of type II fibres

in external intercostal muscle increased in COPD patients.(14) IMT improved inspiratory muscle work capacity by reducing relative work (percentage of maximal muscle work capacity). After IMT, the quantity of cardiac output consumed by the inspiratory muscles decreases; as a result, a larger portion of cardiac output can be redirected to peripheral muscles, thereby increasing exercise capacity.[15]

Gosselink et al. conducted a meta-analysis of 32 randomized controlled trials (RCTs) on the impacts of IMT in patients with COPD. The authors performed general and subgroup analyses of training mode (resistance strength and the inclusion of pulmonary rehabilitation) and subject characteristics. IMT increases inspiratory muscle strength, functional capacity, dyspnea, and quality of life, according to the authors. IMT utiliszed in pulmonary rehabilitation programs improved inspiratory muscle strength and exercise performance in participants with inspiratory muscle weakness.[16] However, the impact of IMT implemented in COPD remains unclear. This scoping review summarizes the existing studies relating to the potential application of IMT in COPD patients.

Objectives

The purpose of this scoping review is to identify and assess the literature on inspiratory muscle training in COPD. What improvements or effects have been reported for COPD patients who train their inspiratory muscles?

Search Strategy

Using the Joanna Briggs Institute (JBI) methodology for scoping reviews, the researchers conducted a scoping review. The databases searched for scholastic peer-reviewed articles included PubMed, Academic Search Complete/EBCSCO, and Google Scholar, in addition to Grey Literature sources.

Studies evaluating the effect of inspiratory muscle training on COPD patients that were published between January 2018 and January 2023 are included. One reviewer extracted the data, and the second reviewer verified thirty percent of the studies.

A preliminary search of PubMed, Academic Search Complete/EBCSCO, and Grey Literature sources, including Google Scholar, was conducted, followed by an analysis of the text words in the title and abstract, as well as the index terms used to describe the articles. The identified keywords and index terms were then utilized in a second search of relevant databases. Thirdly, the reference lists of chosen studies were combed for additional pertinent articles. All studies, regardless of publication date, were considered for inclusion in the review. There was also consideration for including translated studies in the review. The search criteria contained two components. The first construct pertained to the population and was restricted to COPD patient-focused studies. The second construct was limited to inspiratory muscle

training and related to the intervention. The inquiry was conducted utilizing a combination of the two concepts.

Inclusion and Exclusion Criteria

Inclusion criteria were studies examining the short- and long-term effects of inspiratory muscle training on stable or acutely exacerbating COPD patients. The studies must include at least one of the following outcomes: dyspnea, quality of life, exercise capacity, or maximal inspiratory pressure (PImax). This evaluation was limited to randomized controlled trials (RCT).

Not included in the exclusion criteria were sample size or the absence of a control group. Two researchers (ZF and IS) evaluated the title and abstract to identify potentially relevant articles. Inconsistencies were resolved through consensus or consultation with a third investigator.

Quality Rating

Using standardized critical appraisal instruments for Randomized Controlled Trials from JBI to determine the extent to which studies addressed the likelihood of bias in design, conduct, and analysis served as the basis for determining methodological quality.

Result

Initial investigation yielded 644 studies. After removing duplicates (102) of the result of searching, it remained 542. Both evaluators screened all titles solely for relevance, resulting in the selection of 117 articles and the exclusion of 385. Then, both evaluators (IS and ZF) evaluated all titles and abstracts in Rayyan, resulting in the exclusion of 135 articles and the retention of 26. The full-text versions of the included articles were obtained. The reviewers excluded 17 studies due to ineligibility requirements. No authors were contacted for further details. In accordance with the PRISMA Diagram (Figure 1), nine articles remained for inclusion in the present investigation.

Synthesis of Results and Methods of Analysis

Included were nine journal articles with peer review. The characteristics of the study (author, year, study design, population results, and conclusion) are outlined in Table 1. There are provided narrative descriptions of the investigations. The search was designed to be exhaustive in order to cover the current literature, and the included studies were published from 2018 to 2023.
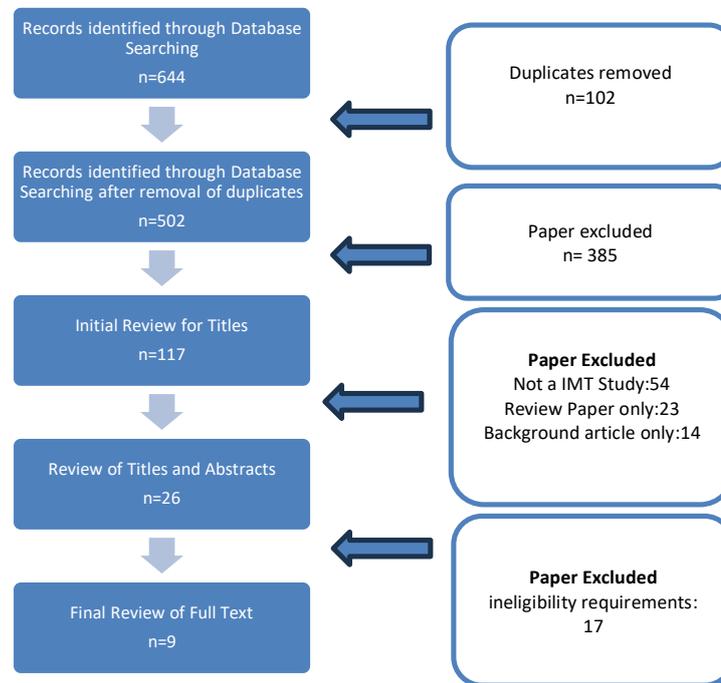
Figure 1 PRISMA diagram.[17]

Table 1 Study Characteristics (Design, Type, Population and Primary Outcomes)

Author	Year	Study Design	Population	Outcomes Measures	Results
Noppawan Charususin, et al. [18]	2018	Randomized Control Trial (RCT)	With inspiratory muscular weakness (Pimax: 5115 cm H2O) and cOPD, 219 patients were randomly assigned to either the intervention group (iMt+Pr; n=110) or the control group (Sham- iMt+Pr; n=109).	• 6MWD • Respiratory Muscle Function • Endurance Cycling Time	Adjunctive iMt-induced improvements in respiratory muscle function did not result in further gains in the main endpoint, the 6MWD. Additional increases in endurance time and decreases in dyspnea symptoms were seen during an endurance cycling test (secondary outcome).

Marc Beaumont, et al. [19]	2018	Single-Blind Randomized Controlled Trial	149 patients with severe or very severe COPD (FEV1 50% expected) were divided into two groups: PRP+IMT (n = 74) and PRP alone (n = 75).	• Dyspnoea (using the Multidimensional Dyspnoea Profile questionnaire at the end of a 6-min walk test (6MWT) at 4 weeks • The Borg (end of the 6MWT) • Modified Medical Research Council scales and in functional parameters (maximal inspiratory pressure (PImax), inspiratory capacity, 6MWT and quality of life)	Dyspnoea significantly decreased in both groups, although there was no statistically significant difference between the two groups in terms of the improvement. When comparing IMT+PRP versus PRP alone, the only statistically significant increase in PImax was seen.
Konrad Schultz, et al. [20]	2018	Randomized Controlled Trial used a parallel group design	Following high-intensity interval-based IMT (n=281) versus sham IMT (n=280) was assigned to 561 COPD patients (medical history of COPD, forced expiratory volume in one second (FEV1)/vital capacity 70%, and FEV1% pred 80% post-bronchodilation).	• Maximal Inspiratory Pressure (Pimax) • 6-Min Walk Distance, • Dyspnoea • Quality Of Life • Lung Function	PImax and FIV1 are improved when IMT is routinely included to a 3-week intense pulmonary rehabilitation programme. Functional ability, dyspnea, or quality of life were not further improved by IMT.
Yasemin Buran, et al .[21]	2022	Prospective single-blind randomized trial	Only IMT (n = 30) or MT above IMT at 40% of maximum inspiratory pressure (MIP) (n = 30)	• Functional Capacity • Respiratory Muscle Strength • Pulmonary Function • Dyspnea • Fatigue • Quality Of Life	The IMT + MT group outperformed the IMT alone in terms of functional capacity, respiratory muscle strength, pulmonary function, dyspnea, tiredness perception, and quality of life.

Ana Lídia, Carvalho Cutrim, et al.[22]	2019	Single-Center Controlled Study,with Balanced Randomization	22 COPD subjects joined the study	• Pulmonary Capacities And Inspiratory Pressure • Total Six-Minute Walk Test • Cardiac Autonomic Modulation.	With enhanced vagal modulation (total variability and HF [ms2; adjusted p 0.05]), higher expiratory and inspiratory capabilities, and increased 6-minute walk distance, the intervention group showed improvements in cardiac autonomic modulation.
Rodrigo Koch, et al. [23]	2020	Prospective Randomized and Cross-Over Study	Prior to and following 10 sessions of high intensity IMT (three times per week) over the course of 30 days nine COPD, subject performed a total of four identical constant work rate tests on a cycle ergometer at 75% of maximum work rate white using proportional assisted ventilation (PAV, individually adjusted) or control ventilation (SHAM, 4cm H_2O)	• Borg Scale • Maximal exercise tolerance • Respiratory pattern	IMT added before PAV-supported aerobic exercise improves exercise tolerance, relieves dyspnea, and causes positive changes in the ventilatory pattern during high-intensity training in patients with severe COPD.
Daniel Langer et al.[24]	2018	Prospective single-blind randomized trial	Twenty participants were randomly assigned to either IMT or a sham training control group (n=10), with FEV1 values of 47 and 19% predicted, Pimax values of 59 and 14 cmH2O, and cycle ergometer peak work rates of 47 and 21% anticipated.	• Lung Function, • Respiratory Muscle Strength, • Activity-Related Dyspnea, • Exercise Capacity	IMT improved mechanically weakened individuals with COPD and low Pimax's strength and endurance of the inspiratory muscle.

Bilel Tounsi et al.[25]	2021	Prospective single-blind randomized trial	32 male patients (age range, 62+ 6 years) with moderate to severe COPD. They were randomly allocated to either the control group (ET) with 16 members or the experimental group (IMT+ET) with 16 members, both of which had comparable features.	• Functional balance was assessed by the Berg Balance Scale (BBS), the Timed-up and Go (TUG), the Single Leg Stance test (SLS), and the Activities- specific Balance Confidence (ABC) scale • The strength of the inspiratory muscles (PI_{max}) was assessed by maximal inspiratory mouth pressure. • Functional exercise performance was assessed by the 6 minutes walking test (6MWT)	According to BBS and ABC, the results show that IMT in addition to ET enhances inspiratory muscle performance and functional balance in COPD patients when compared to ET alone.
Wenhui Xu et al.[26]	2018	Prospective single-blind randomized trial	In 92 individuals, inspiratory muscle training (IMT), combined inspiratory and expiratory muscle training in the same cycle (CTSC), or combined inspiratory and expiratory muscle training in separate cycles (CTDC) were randomly and evenly allocated.	• Respiratory Muscle Strength	While IMT alone just raised PImax, CTSC and CTDC improved the strength of the inspiratory and expiratory muscles.

Discussion

Improvements in the 6MWD (the primary outcome) did not differ statistically significantly across groups in the study of Noppawan (2018). Contrarily, patients in the intervention group significantly improved their ability for endurance exercise and respiratory muscle function (the secondary target that was predetermined). During the cycling test, it was also discovered that the intervention group had much less

symptoms of dyspnea. The significance of external effort and power as training quality attributes of the training stimulus given to the inspiratory muscles is emphasized by this study. The magnitude of PImax increases was not significantly correlated with training volume or compliance (number of training sessions completed). Surprisingly, they found that the number of training sessions combined with the total amount of labour completed (representing pressure and volume responses throughout individual sessions) was the greatest predictor of PImax increases in a multiple regression model (see online supplementary table E5). This emphasizes how important it is to assess training quality (total work done) during IMT to ensure that training adaptations in response to the intervention are efficient.[18]

Dyspnea was improved in both groups in the second randomized controlled trial comparing the effect of IMT during a pulmonary rehabilitation program to a pulmonary rehabilitation program without IMT in patients with severe or very severe COPD, but the difference in dyspnea was not found to be different, even in the subgroup of patients with inspiratory muscle weakness (PImax 60 cm H2O). The two groups' improvements in quality of life and 6MWD were not substantial between the groups. Only in the IMT group paired with pulmonary rehabilitation did PImax improve significantly more than in the pulmonary rehabilitation group. [19] By boosting type II fibers, IMT has the ability to increase diaphragmatic velocity, [14], shorten the inspiratory duration [27] as well as prolong expiratory time, which might lessen hyperinflation (as shown by changes in inspiratory capacity during effort).(28,29) Therefore, IMT may lessen dynamic hyperinflation and, consequently, dyspnea in individuals with severe COPD by increasing PImax.

In comparison to sham IMT, patients with moderate to severe COPD showed a significant improvement in PImax and FIV1, according to the main findings of the third RCT. However, other clinically significant outcomes, such as dyspnea, QoL, functional capacity, and other lung function parameters, did not show a similar improvement. The intervention group's mean increase in PImax of 0.94 kPa (9.59 cmH2O) compared to the control group's corresponds to a PImax mean difference of 8.60 cmH2O, which was made possible by much longer outpatient programs. No additional improvements in clinical outcomes were found despite notable increases in PImax. [20] There might be numerous causes for this. First, the causal model could just be incorrect, and improvements in clinical PImax might not translate into clinical outcomes.[30] However, a number of studies contrasting IMT alone with controls discovered modifications in clinical outcomes. (16,31,32) Second, a 0.94 kPa influence could be negligible enough to result in clinically significant benefits in pulmonary rehabilitation. Longer-term measures are thus needed. By using a 6-month intervention, MAGADLE et al., for instance, showed larger results in PImax as well as effects in functional ability. [33] Third, changes in PImax may only alter clinical outcomes if no other drugs are concurrently affecting them. As a result, prospective IMT benefits may be hidden by the impact of

pulmonary rehabilitation on clinical results. Fourth, various patient subgroups (such as female patients vs. male patients) may react to IMT differently.

In contrast to the meta-analysis of GOSSELINK et al., PImax at baseline did not lessen the severity of the influence on PImax.[16]Regardless of PImax changes, patients with high PImax levels at T0 benefit considerably from the intervention. Furthermore, none of the secondary outcomes were impacted by baseline PImax. As a result, the third trial does not support the idea that IMT is exclusively beneficial for people who have weak inspiratory muscles. The discrepancies in the results of the two studies may be explained by using different methods. While we looked at correlations between patient characteristics, GOSSELINK et al. examined associations between study components (such as mean baseline PImax and mean impact of IMT).[16] If patients are not chosen at random from the same population, which is difficult to verify, inferences from the research to the patient level may be misleading.[30] This reasoning supports the validity of those findings, as does the large sample size of our study. The mean 6MWD increased by more than 80 m in both research arms, both statistically and clinically. The AMD between groups in the ITT analysis was 1.9 m. The per-protocol analysis indicates that IMT may increase females' 6MWD by more than 13 m (Cohen's d=0.21). It is uncertain why the results of the per-protocol analysis and the ITT differ. As a result, the results of the per-protocol analysis should be regarded with caution. Based on the ITT analysis, we conclude that sex had no moderating effect on 6MWD. [20]

For Quality of Life (QoL), similar results were seen. With moderate to large effect sizes, both groups significantly improved, although IMT had no further effects. However, Hosp_Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and sex both impacted quality of life.[20] Men and patients with AECOPD tended to have little benefit or even worsening effects, while extra IMT seemed to enhance females on various QoL subscales. For possible power reasons, no earlier investigation has produced comparable findings. The sex impact is explained by a number of reasonable explanations. For instance, female inspiratory muscles may deplete more gradually.(34,35) Females could experience IMT less stressfully as a result, and they might gain more benefits from the rise in PImax in terms of QoL. Furthermore, "relaxation breathing" (control group) may benefit men more than women. Breathing slowly and steadily for 21 days can be similar to relaxation training. [36] This may have an effect on psychological but not physiological characteristics.[37] However, all of the effects are minor, and the clinical significance is unknown.

Furthermore, it was discovered a considerable improvement in FIV1. Despite the fact that numerous studies showed that the alterations in FIV1 are important,[38] the clinical relevance of a 100 mL difference is unknown, particularly as other lung function metrics did not improve.

The Fourth Study found that a 12-week IMT with MT program increases functional capacity, respiratory muscle strength, pulmonary function, and overall Quality of Life in COPD patients while decreasing dyspnea and tiredness perception. The research found that when pulmonary rehabilitation included MT, FVC improved. [21] Changes in the elastic characteristics of the lungs and chest wall cause an increase in static hyperinflation under certain situations. Expiration towards relaxation volume gets progressively longer as airway resistance and flow constraint increase, and the following inspiration starts before relaxation volume is attained. This exerts an additional stress on the inspiratory muscles at the end of exhalation: they must overcome an additional "threshold" load associated to the respiratory system's elastic rebound before inspiratory flow begins. Furthermore, this happens despite the inspiratory muscles' decreasing mechanical advantage.[39] The addition of MT to IMT enhanced inspiratory muscle strength and endurance more than IMT alone, and it has the potential to reduce the oxygen cost of voluntary hyperpnea and ameliorate patients' reported dyspnea. [40]

The Fifth Study examined how breathing capacity, exercise tolerance, and autonomic function in COPD patients changed after 12 weeks of IMT at 30% of maximal inspiratory pressure (PImax). Our study's key conclusion demonstrates that a regular IMT programme was successful in increasing the maximum strength of the inspiratory and expiratory muscles, cardiac autonomic modulation, and functional capacity as assessed by the 6MWT in COPD individuals. The IMT procedure, however, did not demonstrate significant gains in respiratory function. [22] They discovered that the IMT protocol increases the linear indexes SD1, SD2, and vagal modulation in the frequency domain by increasing HF (ms2) and in the time domain by improving RMSSD, total power, and SDNN, indicating an increase in overall variability in the subjects who underwent the IMT protocol. [22] One of the main mechanisms causing the decreased HRV in COPD is hypoxia. It is plausible that the present intermittent hypoxia in COPD patients is the root cause of autonomic dysfunction. [41] The findings also suggest that sympathetic activity predominates in autonomic dysfunction, which has a significant impact on inflammatory responses.(42,43) Other studies found a substantial negative correlation between blood IL-6 levels in COPD patients and the parasympathetic modulation index (pNN50). [44] These findings may be explained by the fact that IMT increases pulmonary vagal afferents while inhibiting sympathetic activity. In addition, IMT may increase oxygen supply due to tidal volume augmentation while decreasing chemoreflex activity and sympathetic activity. [45,46]

In the sixth study, in severe COPD, adding IMT before a PAV-supported aerobic session improves exercise tolerance and dyspnea alleviation, as well as generates favourable alterations in the ventilatory pattern during high-intensity training. [23]

The main conclusions of the seventh study were that, compared to the control group, 8 weeks of home-based IMT was associated with improved diaphragmatic strength, decreased EMGdi/EMGdimax ratios, and ratings of exertional dyspnea intensity.[24] The results support the idea that perceived dyspnea during exercise in COPD is caused by a higher ratio of diaphragmatic activation to maximum, which may be treated with IMT. It is believed that the higher central motor command output from the cortex necessary to create a certain force or tension by a weaker muscle is what causes the impression of greater perceived muscular effort to occur when any skeletal muscle is impaired (either experimentally or as a result of illness). It has not been conclusively proven that afferent signals from weaker muscles contribute proportionately to perceived effort, and such research present technical challenges. A significant increase in EMGdimax following similar magnitude IC manoeuvres pre- and post-IMT accounted for the majority of the decrease in the EMGdi/EMGdimax ratio. Due to a combination of increased strength and potential neuronal adaptations that facilitated motor unit recruitment during the 8-week training period, the training-induced increase in EMGdimax may reflect a greater ability to recruit more motor units during maximal voluntary diaphragmatic activation.[47,48] The decrease in tidal inspiratory EMGdi is in line with a reduction in the number of motor units required to generate a given force as a result of muscle hypertrophy. [14,47,48]

Eight studies revealed that with the addition of IMT to ET, the berg balance scale (BBS) score improved by 2.7 points, and the activities-specific balance confidence (ABC) scale increased by 7.2%. In both groups, they discovered marginally significant correlations between inspiratory muscular strength and BBS and ABC, but only in the experimental group. According to BBS and ABC, the experimental group (IMT+ET) exhibits a significant improvement in functional balance. [25] According to Ferraro et al., it might be explained by a hypothetical physiological mechanism(s) through which IMT administered to ET improves balance. The first proposed mechanism is based on the stimulation of the diaphragm and intercostal muscles to respond to a different movement in varied activities and at a different frequency, apparently to maintain balance during rapid and unsteady upper body motions. According to Ferraro et al., it might be explained by a hypothetical physiological mechanism(s) through which IMT administered to ET improves balance. The first proposed mechanism is based on the stimulation of the diaphragm and intercostal muscles to respond to a different movement in varied activities and at a different frequency, apparently to maintain balance during rapid and unsteady upper body motions. [51,52]

The second possibility is based on intra-abdominal pressure. This pressure is known to rise when the vertical load on the body rises during walking or running.[53] This significant intra-abdominal pressure may aid to extend the lumbar spine and manage its direction.[53] In order to sustain the increase in intra-abdominal pressure during postural/trunk movement, the diaphragm and abdominal muscles co-activated. The

diaphragm is therefore assumed to support trunk postural control by elevating intraabdominal pressure.[53] The idea that strengthening the inspiratory muscles improves functional balance and may help restore the equilibrium that seems to have been lost due to increases in trunk muscular activity is supported based on these probable physiological pathways.

In the ninth investigation, they found that, although IMT alone had no discernible effect on PEmax, two forms of combination training might enhance both inspiratory and expiratory muscle. We also showed that breathing pattern improvement in COPD patients may be possible with respiratory muscle training, with the effect being more obvious in individuals with weak inspiratory muscles.[26] More research into the physiological mechanisms behind the interactions between the various training components is necessary since the CTSC group's breathing frequency was much lower.

The mechanism that restricts airflow while engaging the expiratory muscles is still somewhat uncertain, caused nonspecific response to increased respiratory stimulation likely caused the expiratory muscle to contract during exhalation.[54] The abdominal muscle is activated during expiration, maintaining the diaphragm muscle's fibre length and force-generating capacity despite lung hyperinflation.[55] As a result, problems with the expiratory muscles might lead to exhaustion in the inspiratory muscles.

Conclusion

Multiple studies on inspiratory muscle training (IMT) in patients with COPD were reviewed. Overall, IMT had mixed effects on various outcomes in COPD patients. Nonetheless, numerous studies demonstrated that IMT can enhance COPD-related outcomes, including respiratory muscle function, dyspnea symptoms, quality of life, autonomic function, exercise tolerance, diaphragmatic strength and reduced exertional dyspnea, and balance.

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