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Open Access Original Article

Serum Zinc and Copper in Children with Febrile Seizures in Basrah, Iraq

DOI: https://doi.org/10.32007/2501-5

Basher Abdullah Jaber* **MBChB , MD**
Sawsan Issa Habeeb** **FICMS**

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Abstract:

Background: Trace elements are essential micronutrients that exist in very low concentrations in the body. They play an important role in various physiological processes and are crucial for proper functioning of the immune system. Many studies have shown that some micronutrients may have a role in febrile seizure such as selenium, zinc and copper.

Aim: To determine the level of serum zinc and copper in children with febrile seizures and explore their relation to selected patients' variables.

Methods: The study included 66 infants and children with simple febrile seizures with two control groups; a febrile control group which includes (62) children with febrile illnesses who were admitted to emergency department at Basrah Maternity and Children Hospital and Basrah General Hospital from the 1st of March to the end of October 2013, and a healthy control group which includes (58) children. Serum zinc and copper were measured for all infants and children enrolled in the study.

Results: Patients with febrile seizure had a significantly lower mean serum zinc level (8.85 ±3.26) in comparison to febrile patients and healthy children (14.98 ±2.20), (13.33 ±1.99) respectively. There is no significant association between the level of serum zinc and selected variables. Serum copper level did not show a significant difference between patients with febrile seizures and control groups.

Conclusion: Zinc supplementation may be considered in children who are at risk of recurrent febrile seizure.

Keywords: Zinc, copper, febrile convulsions.

Introduction

Febrile seizure (FS) is the most common form of seizures in children. (1) The pathophysiology of febrile seizures is still not fully understood. Several theories regarding possible metabolic changes during the rising phase of body temperature have been proposed, such as electrolyte disturbances, relative vitamin B6 deficiency, and low gamma aminobutyric acid (GABA), but these factors do not explain the seizure in the majority of cases.(2) Many studies have shown that some micronutrients may have a role in febrile seizure such as selenium, zinc and copper. (3,4) Copper (Cu) is an essential element in the synthesis and functioning of the nervous system and its deficiency may lead to several complications such as mental disorders, peripheral neuropathies and myelo- neuropathy. Severe copper deficiency may lead to seizure attack based on the important role of copper in cell physiology, such as free radical scavenging, membrane stability and prevention of paroxysmal discharge.(5) Zinc is an important micronutrient that plays important roles in growth and development, immune system response, neurological function, nerve impulse transmission, and hormone release.(6)

**Basra Health Directory, Email:basher.mf50@gmail.com*
*** Basrah Medical College, Email sawsan19612000@yahoo.com*

Zinc can be released by electrical stimulation and may serve to modulate responses at receptors for a number of different neurotransmitters. These include both excitatory and inhibiting receptors particularly N-methyl-D-aspirate (NMDA) and Gamma aminobutyric acid (GABA) receptors. The levels of GABA depend on the level of zinc, as well as zinc is involved in the maintenance of pyridoxal phosphate concentrations by the activation of pyridoxal kinase, the lack of this enzyme results in reduced brain GABA levels. (7)

Methods:

A case-control study has been carried out to determine level of serum zinc and copper in children with febrile seizures. Sixty six patients were recruited in the study, their ages ranged from 6-60 months; (36 males and 30 females) who were admitted to the emergency department at Basrah Maternity and Children Hospital and Basrah General Hospital from the 1st of March to the end of October 2013.

Inclusion criteria

1- Patients with simple febrile seizures, generalized, tonic-clonic attacks lasting for a maximum of 15 min and no recurrence within a 24-hour (8)

2- Absence of central nervous system infections

Exclusion criteria)3, 9, 10, 11)

1- Age younger than 6 months or older than 60 months. 2- History of previous febrile seizure attack(s). 3- Epilepsy and neurologic conditions e.g. (Cerebral palsy). 4- Moderate or severe malnutrition, acute or chronic diarrhea, patients taking zinc supplements for therapeutic purposes within 3 months prior to the study .5- History of chronic diseases such as celiac disease, chronic kidney disease, sickle cell disease and diabetes mellitus. Control groups include: Febrile patients group included 58 febrile infants and children who were seen in the outpatient clinic or emergency department of the same hospitals, because of febrile illnesses as upper respiratory tract infection (URTI), pneumonia, urinary tract infection; no central nervous system infection or history of seizure. Healthy children group included 62 healthy infants and children consulting at Al-Razi and Al-Seef primary health care centers for immunization and routine child health visit. A special questionnaire was designed for the purpose of the study to collect the following information: Identity includes name, age, sex and residence. Presenting symptoms of seizure onset and duration (measured in minutes based on parents' observation record); Fever onset, duration and classified into: low grade fever (37.5 -38.3 °C), moderate grade fever (38.4-38.9 °C), high grade fever (39-40 °C) and hyperpyrexia (>40 °C).(12) Past history of recurrent febrile seizure, Immunization history of recent vaccination within 72 hours, Family history of febrile seizure or epilepsy, (13) Drugs history of oral diazepam, anti-epileptics drug and zinc supplement All patients underwent general and systemic examination, vital signs were measured and anthropometric measurement; weight and height/length were assessed and applied to appropriate charts. An approval from the ethical committee at Basra Medical College and the research committee at Basrah Health Directorate was obtained as well as an informed consent from the parents for all infants and children recruited in the study. Serum Zinc and Copper measurements: Two milliliters of whole blood was collected from the patients during the first 6 hours after admission to hospital and at the time of interview regarding the control groups. (14) The serum was separated and stored at-10°C. Zinc and copper levels were measured by spectrophotometry machine (CE Cell 1011 France made). The normal value for serum zinc is 10.7-17.6 mmol/l, for copper is 0.47-2.36 mmol/l in children up to 10 years), according to the test kit label.

Statistical analysis:

Data was analyzed using SPSS program V.17 Expressed by mean ± Standard Deviation. A comparison of proportions was performed using Chi-Square test. T-test and one-way analysis of variance (ANOVA) was used to compare means. Logistic regression analysis was done to study relation of different variables and for some variables the odd ratio (OR) and 95% confidence interval (CI) were calculated. For all tests P-value of <0.05 was considered as statistically significant.

Results:

A total of 66 children with febrile seizures (FS) were included in the study (mean age was 24.6±13.19 months) . Sixty two healthy children (mean age was 25.1±13.7 months) and 58 febrile children (mean age was 23.8±13 months) were included as controls. The age and sex distribution of the children in the study and control groups showed no significant difference (P value >0.05) as shown in Table 1.Despite higher frequency of upper respiratory tract infections (URTI) and pneumonia seen in patients with febrile seizures and febrile control group, the result were not statistically significant, (P value > 0.05). Although urinary tract infection (UTI) and other causes are seen more frequently in the febrile control group than febrile seizure patients, the result is not significant (P-value > 0.05) as shown in Table 2. Children with febrile seizure had a lower mean serum zinc level (8.85 ±3.26) in comparison to febrile patients and healthy control group (14.98 ±2.20) and (13.33 ±1.99) respectively with statistically significant result (P value < 0.05). No significant differences were detected between febrile and healthy control groups (P value >0.05). The mean serum copper level showed no statistically significant difference between patients with the febrile seizure and control groups (P value >0.05) as presented in Table 3. Table 4 shows no significant correlation between the mean serum zinc level and selected variables of infants and children with febrile seizure such as age, sex, weight and height/length (P value>0.05). Low mean serum zinc level (8.02 ± 2.85 and 8.19 ± 3.03) is seen in children with high grade fever, and those with history of recurrent febrile seizure respectively, with no statistical significance. The mean serum zinc level showed no significant association to family history of febrile seizure. Children with pneumonia had low mean serum zinc level (7.62 ± 2.73) compared to children with other associated illnesses such as URTI or UTI , the difference is not statistically significant (P value > 0.05). There was no significant correlation of studied variables of children with febrile seizure as (age, sex, weight, height, temperature, family history, frequency of FS and diagnosis) with low serum zinc level.

Table 1: Age and sex distribution of patients and control groups

Variable		Febrile Seizure group No. (%)	Control groups Healthy group No. (%)	Febrile patients No. (%)	P-value
Age (months)	6-12	15 (22.7)	17 (27.5)	9 (15.5)	0.87 **
	13-24	26 (39.4)	18 (29.0)	28 (48.3)	
	25-48	20 (30.3)	23 (37.0)	15 (25.9)	
	49-60	5 (7.6)	4 (6.5)	6 (10.3)	
Sex	Males	36 (54.5)	34 (54.8)	31 (53.4)	0.98 *
	Females	30 (45.5)	28 (45.2)	27 (46.6)	
Total (186)		66	62	58	

Table 2: Diagnosis in patients with febrile seizure and febrile control group

Diagnosis	Febrile seizure		Febrile control group		P value*
	No.	%	No.	%	
URTI	31	47.0	23	39.6	0.276
Pneumonia	24	36.4	15	25.9	0.150
UTI	6	9.1	11	19	0.225
Others	5	7.5	9	15.5	0.282

**Chi square test was used to measure P-value for all variables*

Table 3: Mean serum zinc and copper among patients with febrile seizures and controls

Variable	Febrile Seizure group Mean(±SD)	Control groups Febrile group Mean(±SD)	Healthy group Mean(±SD)	P value‡
Zinc	8.85 ±3.26	14.98 ±2.20	13.33 ±1.99	<0.005** 0.182 *
Copper	1.98 ±0.25	1.94 ±0.26	1.88 ±0.43	0.27

‡ ANOVA was used to measure P- value for all variables
*P** patient with FS and control groups (febrile group and/or healthy group)*
P febrile patient and healthy control groups*

Table 4: Serum zinc in relation to selected characteristics of patients with febrile seizures

Variable		Mean Serum Zn	P value**
Age (months)	6- 12	9.24 ± 2.37	0.54**
	13-24	8.73 ± 3.69	
	25-48	8.93 ± 2.87	
	49–60	6.96 ± 1.4	
Sex	Males	8.95±3.29	0.61*
	Females	8.57±2.78	
Weight (Kg)	6-12	8.20±3.02	0.41**
	13-18	9.23±3.10	
	19-24	8.53±2.84	
Height (cm)	60-75	9.42±1.93	0.32**
	76-90	8.20±3.04	
	91–119	9.28±3.80	
Grade of Fever	Low	10.75±0.35	0.13**
	Moderate	10.07±4.20	
	High	8.02 ± 2.85	
Frequency of FS	First attack	9.56 ± 3.41	0.44 *
	Recurrent	8.19 ± 3.03	
Family history of FS	Negative	8.20 ± 3.02	0.34 *
	Positive	9.23 ± 3.10	
Causes of fever	URTI	9.32 ± 2.90	0.135 **
	pneumonia	7.62 ± 2.73	
	UTI	9.88 ± 4.77	
	Other	9.60 ±1.95	

** t- test*
*** ANOVA*

Discussion:

Febrile seizure (FS) is the most common brain related disease in children. (15) Several studies have indicated that multiple factors can be involved in the pathogenesis of febrile seizure. This study was designed to explore whether zinc and copper have any role in developing febrile seizure. A higher frequency of respiratory tract infections was seen in patients with FS and febrile control group; which is in agreement with a study carried out by Al-Zwaini from Iraq, where upper and lower respiratory tract infections constituted 67% of febrile illnesses in children with febrile seizure. (16) In contrast Aliabad et al, (17) found that only 20% of children with febrile seizures had upper or lower respiratory tract infections. The current study showed that the mean serum zinc level was significantly lower in children with febrile seizure compared to the control group. This observation is consistent with studies by Ganesh et al from India (2006), (7) Ehsanipour et al from Iran (2009) (9) and Lee et al from Korea (2012). (18) No significant difference was found regarding the level of serum zinc in relation to age, sex, anthropometric measurements, grade of fever, in consistence with other studies. (7, 9, 18) In addition, no significant difference in mean serum zinc levels was found in relation to family history of febrile seizure, number of convulsions, in agreement with İhsan et al from Istanbul (19). The reason for lower serum zinc levels in patients with febrile seizure is not known. However, fever and acute infections may have some role in developing such conditions. It is believed that the release of tumor necrosis factor (TNF) and interleukin during fever or tissue injury may result in the reduction of serum zinc level (20) Izumi et al (21) and Pallain et al (22) proposed that hypozincemia trigger the N-methyl-D-aspartate (NMDA) receptor which is one of the members of glutamate family receptor, and it may play an important role in the initiation of epileptic discharge. This study did not observe any reduction in the serum zinc levels in children who had fever without seizure. Patients with febrile seizures and pneumonia had lower serum zinc level than children with URTI or UTI, but not significantly so. Many authors have confirmed that routine zinc supplementation for more than three months has a positive effect on reducing the duration of acute lower respiratory tract infections among children in developing countries. (6) On the other hand, a the study conducted by Cho et al. Pusan Hospital in Korea , reported no significant difference between the mean serum zinc level in children with febrile seizures and that of control group , possibly because of the small sample size patients (11) included in their study. (23) A study carried out on 310 children with FS, by Sadeghzadeh et al in Iran did not show a significant correlation between serum zinc level and febrile seizure. (24) Studies carried out to assess the role of copper in febrile seizures are few. (25, 26) Copper deficiency is rather uncommon in humans due to its very low daily requirement and easy consumption in a variety of food items such as legumes, meats and nuts. The current study showed that only (10.6%) of patients had a positive family history of FS, because of enrolment of first degree relatives only in the family history of studied children, (13) in comparison to the higher result which varied from 25% to 40% from other studies. (27) High grade fever was recorded in 80% of patients with FS; other studies demonstrated that the height of temperature was a significant independent risk factor for FS. (28) Other studies found that temperatures more than 38.5○C, are related to recurrent FS with focal features. (27) Serum copper level was not significantly different in FS group compared to the control group. A similar result was found by Mahyar et al. (25) Although studies on the role of serum copper in febrile convulsions are rare, current findings and previous limited research showed that copper probably has no

role in febrile seizures.From this study, it can be concluded that children with febrile seizures have low serum zinc level and possibly zinc supplementation can be considered in patients who are at risk of recurrent febrile seizure.

Authors' contribution:

Dr. Basher Abdullah Jaber ; corresponding auther

Prof. Sawsan Issa Habeeb; supervisor

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مستوى الزنك والنحاس عند الاطفال المصابين بالصرع الحراري

الخلاصة:

خلفية البحث: ان المغذيات الدقيقة الأساسية الموجودة في تراكيز منخفضة جدا في الجسم مثل السيلينيوم والزنك والنحاس تلعب دورًا مهمًا في العمليات الفيسيولوجية المختلفة وتعتبر أساسا في الأداء السليم لجهاز المناعة وقد أظهرت العديد من الدراسات أن هده المغذيات الدقيقة قد يكون لها دور في الصرع الحراري عند الاطفال.

الهدف: تحديد مستوى الزنك والنحاس في الدم لدى الأطفال الذين يعانون من الصرع الحراري ودراسة العلاقة مع بعض المتغيرات لدى المرضى .

المنهجية: شملت الدراسة 66 رضيعاً وطفلا يعانون من نوبات صرع حراري بسيط ومجموعتان ضابطتان؛ وتشمل مجموعة الاطفال الذين يعانون من حمى ومجموعة الاطفال الاصحاء. تم قياس مستوى الزنك والنحاس في المصل لجميع الرضع والأطفال المسجلين في الدراسة.

النتائج: المرضى الذين يعانون من نوبة الصرع الحراري لديهم مستوى منخفض بشكل ملحوظ من الزنك في المصل (8.85 ± 3.26) بالمقارنة مع مجموعتي الضبط "مرضى الحمى والأطفال الأصحاء" (14.98 ± 2.2)، (13.33 ± 1.99) على التوالي. لا يوجد ارتباط ذو دلالة إحصائية بين مستوى الزنك في المصل مع متغيرات المرضى المحددة. لم يُظهر مستوى النحاس في مصل الدم فرقاً معنوياً بين المرضى الذين يعانون من نوبات الصرع ومجموعات الضبط.

الإستنتاج: يمكن ادخال مكملات الزنك في علاج الأطفال الذين هم عرضة لخطر نوبات الصرع الحراري المتكرر

الكلمات المفتاحية: الزنك ,النحاس ,الصرع الحراري.

Etiological factors of cholestasis in infancy and early childhood in Children Welfare Teaching Hospital

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Adnan Y. Mahmood* **MBChB**
Mohammad F. Ibraheem** **MBChB, DCH, FICM, CABP**
Jasim M. Salih*** **MBChB, DCH**

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Abstract:

Background: Neonatal cholestasis is defined as prolonged elevation of the serum level of conjugated bilirubin beyond the first 14 days of life. There are many causes of neonatal cholestasis which must be identified because early intervention may result in a better outcome, such as surgical intervention in biliary atresia within two months from birth, or effective dietary management in metabolic disorders like galactosemia.

Objective: To determine the causes of early childhood cholestasis in children attending the Children Welfare Teaching Hospital in Baghdad and to study some of associated factors in infancy and early childhood cholestasis.

Patients and method: This is a cross sectional descriptive study conducted on 48 patients attending the Children Welfare Teaching Hospital in Baghdad for the period of 1 November 2015 to 15 January 2016. These cases were evaluated by thorough history, examination and investigations.

Results: Of the 48 patients enrolled in this study, 30 (62.5%) lived in Baghdad, and the remaining 37.5% were referred from other governorates. The mean age of the patients was 11.1 ± 12.4 months, with 20 females (41.7%) and 28 males (58.3%). The results revealed that 11 (22.9%) were the result of congenital infections, 9 (18.8%) were idiopathic in origin, 8 (16.7%) were caused by biliary atresia, 8 (16.7%) of unknown origin, 5 (10.4%) were caused by sepsis (mainly *staphylococcus*, *streptococcus species*, *E.coli*, *staphylococcus aureus)*, 2 (4.2%) were caused by progressive familial intrahepatic cholestasis and 1 (2.1%) case was caused by each of the following causes: Alagille syndrome, Choledochal cyst, Galactosemia, hypothyroidism and Tyrosinemia**.**

Conclusion: Congenital infections were the most common cause in this study, of which the most common is cytomegalovirus (CMV). Clay color stool and high alkaline phosphatase levels were found mostly in biliary atresia. No method by itself is sufficient to diagnose the cause of neonatal cholestasis. Diagnosis can only be established using all available methods.

Keywords: Cholestasis, children, etiology.

Introduction:

Neonatal cholestasis is defined as prolonged elevation of the serum levels of conjugated bilirubin beyond the first 14 days of life. Early intervention results in a better outcome such as surgical intervention in biliary atresia before two months and the effective management of disorders like (Tyrosinemia, galactosemia, hypothyroidism, and infectious causes) (1, 2). Cholestasis in the neonate may be the initial manifestation of numerous and potentially serious disorders, the clinical manifestations are usually similar and provide very few clues regarding the etiology (3, 4, 5).

The most common causes of Cholestasis in infancy are biliary atresia (BA) and Neonatal Hepatitis Syndrome (NHS), a term which is given now to nonspecific hepatic inflammation, which develops secondary to many different etiologies including intrauterine infections, endocrine disorders and inborn errors of metabolism (3,6,7). Cholestasis in a newborn can be caused by infectious, genetic, metabolic, or undefined abnormalities giving rise to mechanical obstruction of bile flow or to functional impairment of hepatic excretory function and bile secretion (2, 6-8). Investigations needed to reach the diagnosis can be classified into three main categories (6, 7, 10, and 11): Laboratory studies, imaging studies and percutaneous liver biopsy which is the single most definitive investigation in the evaluation of neonatal cholestasis. Several studies in different centers indicated that a diagnosis of biliary atresia was correctly reached by liver biopsy histological findings in 90 - 95 % of cases (12, 13).

* *Children Welfare Teaching Hospital.* *adnany1984@gmail.com*
** *Department Of Pediatrics, College Of Medicine, University Of Baghdad.*
Correspondence email: *mohammedalqaisi@yahoo.com*
*** *Al-Karkh Health Directorate Baghdad.* *jasimalmawaly68@yahoo.com*

Patients &Method:

This is across sectional descriptive study conducted on 48 patients attending the Children Welfare Teaching Hospital in Baghdad for the period of 1 November 2015 to 15 January 2016. The cases were evaluated by thorough history, examination and investigations. Cholestasis was defined as the prolonged elevation of the serum levels of conjugated bilirubin beyond the 1st 14 days of life greater than 1.0 mg/dl (17.1 micromol/l) if the total serum bilirubin is < 5.0 mg/dl (85.5 micromole/l) or greater than 20% of the total serum bilirubin if the total serum bilirubin is > 5.0 mg/dl (85.5 micromole/l). (1, 2)

Inclusion criteria: All infants with cholestasis persisting beyond two weeks in the neonatal period or cholestasis lasting for four weeks or more in older infants (2). Thorough history was taken including: Gestational age, gender, birth weight, blood group of the mother and the child, age at time of appearance of jaundice, stool color, family history of the same condition or any liver or chronic disease, mother's history of previous abortion or infant death].

Physical examination included: General examination, abdominal examination for organomegaly, ascites, any features of congenital anomalies, and any significant systemic signs or findings. Investigations were done in a stepwise approach. All the patients were sent for general investigations (liver functions: Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, direct and indirect bilirubin level, prothrombin time, and partial thromboplastin time: renal functions: Blood urea and serum creatinine), complete blood picture and blood film, C- reactive protein, blood culture, general urine examination and urine culture, and abdominal ultrasound. Specific investigations as needed include: TORCH screening (IgM and IgG for CMV, Herpes, Rubella, and Toxoplasmosis) conducted in the Central Public Health Laboratory, thyroid function test (T3, T4, and TSH), screening for inborn errors of metabolism which were conducted in Lebanon and ultrasound guided percutaneous liver biopsy for 13 patients when the initial investigations failed to reach the diagnosis and no contraindications were identified to perform the procedure. The study protocol was approved by the Scientific Council of the Arab Board of Pediatrics. Agreement of the hospital administration office was obtained with verbal consent from patients relatives (parents or care-takers). Data of patients was kept in a secured computerized database and was not disclosed to non-authorized persons. SPSS version 20 software was used for data entry and analysis, Standard Chi-square test was used to determine the associations between two categorical variables. Yates correction formula and fishers exact test were applied for chi-square test whenever it was needed, *P* value of less than 0.05 was considered as statistically significant.

Results:

A total of 48 patients were enrolled in this study, with an age range of 4 weeks to 13 months, and a mean age of 11.1 months ± 12.4. There were 20 females (41.7%) and 28 males (58.3%).

Table (1) shows that 11 (22.9%) of the cases were caused by congenital infections, mainly CMV (10 cases - 91%) and Toxoplasmosis (one case - 9%). Idiopathic neonatal hepatitis was found in 9 cases (18.8%), biliary atresia in 8 (16.7%), unknown causes in 8 (16.7%), sepsis in 5 (10.4%) (*staphylococcus aureus*, *streptococcus species*, *E-coli*,), PFIC in 2 (4.2%) and 1 (2.1%) case was caused by each of the following causes: Alagille syndrome, Choledochal cyst, Galactosemia, hypothyroidism and Tyrosinemia.

Table 1:- Distribution of the causes of jaundice in the study group

Causes		Number	%
Infections	Congenital	11	22.9
	Sepsis	5	10.4
Idiopathic Neonatal hepatitis (INH)		9	18.7
Biliary Atresia		8	16.6
Progressive familial intrahepatic cholestasis		2	4.2
Choledochal Cyst		1	2.1
Genetic and Inborn Errors	Alagille syndrome	1	2.1
	Galactosemia	1	2.1
	Hypothyroidism	1	2.1
	Tyrosinemia	1	2.1
Unknown		8	16.7
Total		48	100

A significant association was found between the etiological factors and time of appearance of jaundice, where 81% of the cases caused by congenital infection and 77.8% of the Idiopathic neonatal hepatitis (INH) cases presented within the first week of life while 62.5% of the biliary atresia cases and 60% of the sepsis cases presented on the second week of life, (P-value 0.01), table 2.

Table 2: Distribution of the study group by the cause and age at onset of jaundice

Diagnoses	Total	Age at onset of jaundice				
		<1 week		≥1 week		
		No.	%	No.	%	P-value
Congenital infections	11	9	81.8	2	18.2	0.01
INH	9	7	77.8	2	22.2	
BA	8	3	37.5	5	62.5	
Sepsis	5	2	40.0	3	60.0	

Table 3 shows that the highest most of the cases of jaundice caused by congenital infections or idiopathic neonatal hepatitis presented with intermittent clay colored stool (63.6%, 55.6% respectively), while all cases caused by biliary atresia presented with persistent clay colored stool and all cases caused by sepsis presented with normal colored stool.

Table 3: Distribution of the study group by the cause of Jaundice and stool color

Diagnoses	Total	Stool Color						p-value
		Clay stool		Intermittent clay		Normal		
		No.	%	No.	%	No.	%	
Congenital infections	11	0	0	7	63.6	4	36.4	0.01
INH	9	2	22.2	5	55.6	2	22.2	
BA	8	8	100.0	0	0	0	0	
Sepsis	5	0	0	0	0	5	100.0	

No significant differences were found (P- value ≥ 0.05 for all) with regards to levels of ALT, AST, TSB and direct bilirubin among patients according to different causes of jaundice. The only significant difference was found with Alkaline phosphatase level (p=0.01), table 4.

Table 4: Mean values of liver function indicators according to cause of Jaundice

Liver Function Test	Cause of Jaundice	No.	Mean	SD	p-value
Alanine Amino-transferase (U/L)	Congenital infections	11	144.1	70.7	0.5
	INH	9	56.7	34.9	
	B.A	8	139.0	258.3	
	PFIC	2	78.5	14.8	
Aspartate Amino-transferase (U/L)	Congenital infections	11	201.2	117.2	0.8
	INH	9	130.6	145.2	
	B.A	8	200.1	186.8	
	PFIC	2	102.0	19.7	
Alkaline Phosphatase (U/L)	Congenital infections	11	277.5	203.4	0.01
	INH	9	151.7	140.9	
	B.A	8	692.5	312.1	
	PFIC	2	1183.5	426.1	
Total Serum Bilirubin (mg/dl)	Congenital infections	11	8.1	203.4	0.08
	INH	11	7.6	3.1	
	B.A	9	12.6	3.4	
	PFIC	2	13.5	5.0	
Direct Serum Bilirubin (mg/dl)	Congenital infections	11	6.5	3.2	0.3
	INH	9	6.2	3.2	
	B.A	8	8.6	2.9	
	PFIC	2	10.9	12.7	

Discussion:

In the current study the most common cause of jaundice was congenital infections, followed by Idiopathic Neonatal Hepatitis, biliary atresia, sepsis, and to a lesser extent by genetic causes and inborn errors of metabolism. Eight cases were considered of unknown origin even after thorough investigations. This is in agreement with a study conducted in India by Matthai et al (14), in which six out of 14 cases with neonatal hepatitis were due to CMV and two were positive for Herpes, both of which are congenital infections. BA was diagnosed in 7 (18.9%), NH in 6 (16.2%), and metabolic causes in 5 cases metabolic causes, and one case due to hypothyroidism. Our results disagree with those of Al-Azzawi et al (15) in Iraq, which shows that BA was the most common cause of cholestatic jaundice diagnosed in 22 cases (44%), followed by Neonatal hepatitis syndrome 17 cases (34%). Our results also disagree with those of Dehghani et al (16) in Iran where BA and INH were diagnosed in 30 cases each (24.6%), followed by paucity of intrahepatic bile ducts in 16 cases (13.1%) as the most common causes of cholestasis, while genetic and metabolic disorders were seen in 8.2%, and progressive familial intrahepatic cholestasis in 4.1% of cases. This disagreement may be due to decline of the standards of antenatal care during the past few years in Iraq as well as the small number of patients who underwent liver biopsy. Eight cases remained as unknown etiology, which may contribute to the lower percentages of both BA and INH. In the current study, CMV infection was found to be the most common cause of intrauterine infections 10 cases (91%), while there was only one case of Toxoplasmosis (9%), in agreement with the findings of Deghady et al (17) in Alexandria who found CMV in 41.4% of their cases, HSV in 10.3%, CMV + HSV in 20.9%, and Toxoplasmosis in 6.9%. And also, this study agrees with Matthai J et al, study(14) ,in India in which Among 8(21.6%) with congenital infections 6(16.2%) were due to cytomegalovirus and 2(5.4%) were positive for Herpes. The center where the study was conducted lacks facilities for advanced metabolic and genetic testing. Many cases did not undergo liver biopsy due to delays in case referral, uncorrectable PT and PTT, and family refusal. As a result, eight cases (16.7%) were considered as unknown cause. The study conducted by Dehghani et al (16) in Iran had 28 cases (22.9%) in which the causes of cholestasis were labeled as "unknown" and the study of Al-Azzawi et al (15) in Baghdad had 9 cases (18%) where no definite cause could be found. In the current study INH was more common in males 7 cases (77.8%) than females 2 cases (22.2%), which agrees with the findings of Wongsawasdi et al (18) in Chiang Mai University, with 13 males and 10 females. We found BA to be also more common in males (5 cases - 62.5%) than females (3 cases - 37.5%) contrasting Wondsawadi where there was 14 males and 17 females with BA. In total, there was a male predominance in our series (28 - 58.3%) compared to 20 females (41.7%). Dehghani et al (16) series had 20 males with INH and only 10 females, while there were 13 males with BA and 17 females. Their series included 122 cases, compared to our smaller 48 cases. The preference of males in our community may have contributed to this finding. In the current study, persistent clay-color stool was seen in all patients with BA, while INH cases had more intermittent clay stool. Dehghani et al (16) had the same finding, with 54 of all cholestasis cases (44.3%) had clay-color stool, 20 out of 30 infants with BA (66.7%) and 12 out of 30 with INH (23.7%) had clay-color stool. Wongsawasdi et al (18) found that acholic and pale yellow stools were significant in BA cases compared to those in NH. Ağın et al (19) in Turkey found that acholic stools were observed in all patients in the BA group but only in 10 cases (37%) in the non-BA group. Sinha et al. (20) found that all patients with BA

presented with varying degrees of conjugated jaundice and pale non-pigmented stools. The onset of jaundice in the current study was more frequent during the first week of life in INH cases while in BA cases it happened mainly after the first week of life. This was helpful in identifying the causes of the disease. Dehghani et al (16) found no significant correlation between the age of jaundice onset and the cause of cholestasis. In the current study the S-ALP mean level showed a significant difference mainly between the BA and INH, with the higher level being in favor of BA rather than INH. Total and direct serum bilirubin levels and both S-ALT, S-AST were not significantly different, in agreement with Al-Azzawi et al (15). Deghady et al (17) found that transaminases were specific in differentiating BA from NH or other causes of cholestasis but did not address the differences in S-ALP level. Dehghani et al (16) found no differences in S-ALP level between different types of cholestasis.

Conclusion:

Congenital infections are the most common cause of cholestasis.

CMV infection is the most common cause of intrauterine infections.

Persistent clay color stool and high alkaline phosphatase levels are found mostly in Biliary Atresia.

No method by itself is sufficient to diagnose the cause of neonatal cholestasis. Indeed, diagnosis can only be established using all available methods.

Authors' Contributions:

Dr.Mohammad Fadhil Ibraheem: Conceived and designed the analysis, perform the analysis, and wrote the paper.

Dr. Adnan Yahya Mahmood: collect the data, perform the analysis, and wrote the paper.

Dr. Jasim Mohamed Salih: collect the data, perform the analysis, and contribute data and analysis tool.

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العوامل المسببة لحدوث الركود الصفراوي في الطفولة المبكرة في مستشفى حماية الأطفال التعليمي

د. عدنان يحيى محمود
د. محمد فاضل إبراهيم
د. جاسم محمد صالح

الخلاصة:
الخلفية: يتم تعريف الركود الصفراوي لحديثي الولادة على أنه ارتفاع مستمر في مستوى المصل من البيليروبين المترافق بعد الأيام الـ14 الأولى من الحياة. هناك العديد من الأسباب لحدوث الركود الصفراوي لحديثي الولادة ويجب تفريقها عن بعض لأن التدخل المبكر قد يؤدي إلى نتيجة أفضل مثل التدخل الجراحي في رتق القناة الصفراوية في غضون شهرين من الولادة والتدبير الفعال للاضطرابات الأخرى القابلة للعلاج مثل أرتفاع الجالاكتوز في الدم وبدء العلاج في وقت مبكر.
الهدف: تحديد أسباب الركود الصفراوي في مرحلة الطفولة المبكرة في الأطفال الذين راجعوا مستشفى حماية الأطفال التعليمي في بغداد ودراسة بعض العوامل المصاحبة للركود الصفراوي في مرحلة الطفولة المبكرة.
المرضى والمنهجية: دراسة وصفية مقطعية لـ 48 مريض راجعوا مستشفى حماية الأطفال التعليمي في بغداد للفترة من الأول من نوفمبر 2015 إلى الخامس عشر من يناير 2016. وقد تم تقييمهم من خلال التاريخ المرضي والفحوصات السريرية والمختبرية.
النتائج: تم تسجيل مجموعة من 48 مريضا في هذه الدراسة، وظهر أن 30 مريضا (62.5٪) كانوا يعيشون في بغداد أما الباقين فكانوا من محافظات أخرى، وكان متوسط عمر المرضى 11.1 ± 12.4 شهراً. وكان عدد الإناث 20 (41.7٪) والذكور 28 (58.3٪) من مجموعة الدراسة. أظهرت النتائج أن 11 حالة (22.9٪) سببها عدوى خلقيّة، 9 (18.8٪) من الحالات كانت مجهولة السبب، 8 (16.7٪) سببها رتق القناة الصفراوية، 8 (16.7٪) من أصل غير معروف، 5 (10.4٪) بسبب الخمج (المكورات العنقودية بشكل رئيسي، الأنواع العقدية، بكتريا القولون)، 2 (4.2٪) الناجمة عن ركود صفراوي داخل الكبد التدريجي و 1 (2.1 ٪) كان السبب كل من الحالات التالية: متلازمة الاجايل، تكيس الصفراء، أرتفاع الجالاكتوز في الدم، قصور الغدة الدرقية وزيادة التايروسين في الدم.
الاستنتاج: كانت العدوى الخلقية هي السبب الأكثر شيوعًا في هذه الدراسة، وعدوى الفيروس العملاق هي السبب الأكثر شيوعًا للإصابة بالتهابات داخل الرحم, لون الغائط الطيني، ومستويات فوسفاتاز القلوية العالية تكون موجودة غالباً في الرتق الصفراوي. لا تكفي أي طريقة بحد ذاتها لتشخيص سبب الركود الصفراوي عند حديثي الولادة. في الواقع، لا يمكن تحديد التشخيص إلا باستخدام جميع الطرق المتاحة.
الكلمات المفتاحية: ركود صفراوي، الأطفال، المسببات.

Open Access Original Article

Comparison of Three Different Treatment Regimens of HCV Infection in 295 Iraqi Patients

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Wasan K. Jasim AL-Saedi* **FIBMS**
Nawal M. Firhan AL-Khalidi* **CABM, FICMIS**
Ahmed A. Hussein ** **PhD**

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Abstract:

Background: Viral Hepatitis C infection is global public health problem throughout the world. Different treatment regimens are used which produce different rates of response affected by many factors.

Objectives: To assess the efficacy of three different treatment regimens in 295 Iraqi patients infected with chronic HCV.

Patients and methods: This is an observational cohort study; in which 295 (133 male and 162 female) patients with chronic HCV infection were enrolled during the period between August 2015 to January 2017 from Gastroenterology Clinic of Baghdad Teaching Hospital and Gastroenterology and Hepatology Teaching Hospital. Baseline HCV viral load measurements and genotyping were done for each patient. Patients were followed up by viral load measurement at end of the treatment period and three months after the end of the treatment.

Results: The majority of patients infected with chronic HCV achieved sustained virological response(SVR) (defined as undetectable HCV RNA 12 to 24 weeks after the end of the treatment); were of the generic(sofosbuvir/ledipasvir) treatment group (51 out of 72 (70.8%) followed by generic Sofosbuvir with(peg interferon/ribavirin)treatment group (68 out of 111 (61.3%) followed by (peg interferon/ribavirin) treatment group (42 out of 86 (48.8%).

Conclusions: The best treatment efficacy was obtained with generic sofosbuvir/ledipasvir followed by sofosbuvir with peg interferon and ribavirin then peg interferon and ribavirin. The most responder genotype in Iraqi patients was genotype 4 and the least responder genotype was genotype 1b.

Key words: HCV, sofosbuvir, ribavirin, INF

Introduction:

Hepatitis C is an infectious disease caused by hepatitis C virus which is a single strand ribonucleic acid (RNA) virus affecting initially the liver, and may lead to hepatic and extra hepatic complications. The virus can cause both acute and chronic hepatitis infection ranging in severity from a mild illness lasting a few weeks to a serious lifelong illness. (1) Hepatitis C virus includes six major genotypes which determine the type, duration of and response to treatment. Several drugs were developed to treat HCV infection beginning with the use of interferon, addition of ribavirin, using of pegylated forms of interferon and addition of direct antiviral drugs. Recently the HCV treatment guidelines directed towards the use of an interferon free regimens to avoid adverse effects associated with the interferon use.(2) The aim of treatment of HCV infection is to cure the infection, which is measured by sustained virological response (SVR) (defined as undetectable HCV RNA12 weeks to 24 weeks after the end of treatment). Achieving SVR associated with the decrease of hepatic and extra hepatic complications, prevents the spread of the infection and improves the quality of life.(3) New drugs for HCV infection were used to treat Iraqi patients (including sofosbuvir and sofosbuvir/ledipasvir combination). These drugs are of generic origins. There is need to study the efficacy of these drugs in the treatment of HCV infected Iraqi patients.

** gastroenterology and hepatology diseases hospital.*
Corresponding email: wsnali2010@gmail.com
Nawalgastro @gmail.com
*** College of Pharmacy, University of Baghdad.*
Email: ahmed_sura@yahoo.com

Patients and Methods:

Study design and settings: This is a comparative study of three treatment regimens conducted at the Gastroenterology and Hepatology Teaching Hospital

and Baghdad Teaching Hospital of the Medical city – Baghdad - Iraq from August 2015 to January 2017.
The study included 295 naive adult patients (133 males and 162 females) with chronic HCV infection (over 18 years of age).

Exclusion criteria were:
Conditions related to the liver: acute infection; co-infection with other viruses (HBV or other liver infecting viruses); liver cirrhosis; or liver transplanted patients, immune system conditions: patients using immune modulator drugs like systemic steroid, interferon, interleukins or cytokines; patients with autoimmune diseases; or immunocompromised, patients with co-morbidity: Renal impairment; malignancy; or thalassaemia, conditions related to the treatment: patients who had no measurement of viral load before and at the end of treatment; patients who stopped treatment or were non-compliant because of side effects or due to any other cause; or patients who failed on previous treatment regimens and others: Pregnant women; or alcoholic patients.

Patients:
Two hundred ninety five patients with chronic HCV were enrolled in this study, and were randomly distributed by a specialist physician into three groups according to the treatment regimen they received, taking into consideration the cost and availability of the drugs. In August 2015, two regimens were used, which were:
1- Peginterferon with ribavirin group (PR): 92 HCV infected patients who underwent PR treatment for 48 week of peg-IFN - alfa-2a prefilled syringe subcutaneously in a dose of 180 mcg once a weak or peg-IFN - alfa-2b prefilled syringe subcutaneously in a dose of 1.5mcg/kg/week with ribavirin 200 mg capsule in a dose calculated according to body weight: Those ≥ 75kg received 1200mg daily and those < 75 kg received 1000mg daily. Both peg interferon and ribavirin might be given in dose modification later on according to their adverse effects. The study began in 2015 and the guidelines at that time permit use of PR regimen.
2- Pegintrferon with ribavirin and sofosbuvir group (SOF+PR): 125 HCV infected patients were given peginterferon with ribavirin in a dose similar to first group with addition of sofosbuvir 400mg tablet daily for 12 weeks period.
Then in 2016 sofosbuvir with ledipasvir were prescribed to HCV infected patients who were included later in this study.
3- Sofosbuvir and ledipasvir group (SOF/LDV): 78 HCV infected patients were given sofosbuvir 400mg and lepasvir 90 mg as a single tablet per day for 12 weeks.
Patients were followed up for 48 weeks for the first regimen and for 12 weeks for second and third regimens by the measurement of viral load before and at the end of the treatment (ETR), and 3 months after the end of treatment (SVR). Twenty six patients were lost to follow up by SVR, for different reasons (6 patients of PR group, 14 patients of SOF+PR group and 6 patients of SOF/LDV group).

Ethical consideration: Participants agreed to participate in this study after being prepared to understand the aims of the study.
This study was submitted to Iraqi Board for Medical Specializations / Clinical Pharmacy Board.

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Sample collection and processing: Five milliliters blood samples were collected from patients suspected of having HCV in sterile test tubes. The samples were processed and analyzed in the serology section of the G.I.T Center at the Medical City Teaching Hospital. The sera were separated and screened for HCV antibodies by using HCV ELISA test kit which utilizes antigens from the core, NS3, NS4, and NS5 regions of the virus. Antigens have been carefully developed and selected to provide a sensitive and specific diagnostic test. Positive serum was stored in (-20◦C) unit test for viral load. HCV viral load measurement was done in the private Nursing Home Hospital and Gastroenterology and Hepatology Hospital in the Medical City and in Dubai private laboratory while genotyping was done in Dubai private laboratory only. HCV detection by polymerase chain reaction (PCR) is based on the amplification of specific sites of the pathogen genome. In real-time PCR the amplified product is detected by fluorescent dyes. These are usually linked to oligonucleotide probes that bind specifically to the amplified product. Monitoring of fluorescence intensities during the PCR run (i.e., in real time) permits the detection and quantitation of accumulating product without having to re-open the reaction tubes after the PCR run. HCV RNA viral load was determined following the manufacturers recommendations by a sensitive PCR based assay (COBAS amplicor; ROCHE diagnostic.Kit: COBAS®AmpliPrep/ COBAS TaqMan® HCV Quantitative test, v2.0) manufactured by Roche /Germany. HCV genotyping test was done based on reverse-hybridization standard; biotinylated amplicons, generated by RT-PCR of the 5,UTR and Core regions of HCV RNA, are hybridized to specific probes that are bound to nitrocellulose strip by a poly-T tail; biotinylated hybrids are then detected using streptavidin bound to alkaline phosphatase; ampilicons that are not complemented are washed out. Then the substrate reacts with the streptavidin-alkaline phosphatase complex forming purple precipitate and coloring banding pattern on the strip (the instrument used was Rotor-Gen Q manufactured by Qiagen Hiden-Germany and the kit used was (GEN-C 2.0 manufactured by nuclear laser medicine S.r.i (Italy)).
Although measurement of viral load is important after one month of treatment, the study does not include this measurement in order to reduce the cost for the patients.

Medication manufacturing origin:PR treatment regimen were 100% (n=92) of American origin in this study while sofsbuvir in SOF/PR regimen 50.4% (n=63) were from Indian origin and 44.8% (n=56) were from Egyptian origin; SOF/LDV regimen 84.5% (n=65) were of Indian origin and 11.3% (n=9) were of Egyptian origin.

Statistical analysis: Each patient was assigned a serial identification number. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 19. The continuous data were represented by median and inter quartile range. The categorical data presented as frequency and percentage tables; Binary logistic regression was used to assess the association.

Continuous data were tested for normality by Kolmogorov – Smirnov test. Non-normally distributed data were analyzed using nonparametric tests (Mann-Whitney U test, Median test, Wilcoxon test).

Categorical data were analyzed using the Chi-square test; P – value less than 0.05 was used as the alpha level of significance.

End point: Compare sustained virological response of the three different regimens

Results:

Baseline characteristics of the study population:

Female represented 51.1% of the PR group, 51.2% of the SOF+PR group, while in SOF/LDV group they represented 65.4%, but this was statistically non-significant. The median age of patients in the three groups did not differ significantly which was: 36 years for PR group, 39 years for SOF+PR and 38 years for SOF/LDV. Moreover, viral load measurements were not statistically different at baseline. Laboratory test including (White Blood Cells, platelets, granulocytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALK), Albumin, Total serum. bilirubin (TSB), international normalized ratio (INR), Random blood sugar (RBS), Blood urea, and Serum creatinine) were not statistically significantly different, except for the hemoglobin (p value 0.017)} which was statistically significantly different (Table 1(a),(b)).

Table 1(a): Baseline characteristic of categorical variables of the study population

Variable		PR	SOF+PR	SOF/LDV	
		No. (%)	No. (%)	No. (%)	P*-value
Gender	Female	47 (51.1%)	64 (51.2%)	51 (65.4%)	0.096
	Male	45 (48.9%)	61 (48.8%)	27 (34.6%)	
Viral load	<800000 iu/mL	54(58.7%)	74(59.2%)	57(73.1%)	0.087
Viral load	≥800000 iu/ml	38(41.3%)	51(40.8%)	21(26.9%)	

*Chi-square test (P-value significant at alpha<0.05)
PR: PEG-IFN-alfa-2a or alfa-2b + ribavirin,
SOF + PR: Sofosbuvir + peg-IFN-alfa-2a or alfa-2b + ribavirin,
SOF/LDV: Sofosbuvir + ledipasvir

Table 1(b): Baseline characteristic of continuous variable of the study population

Variable	PR	SOF+PR	SOF/LDV	
	Median (IQR)	Median (IQR)	Median (IQR)	P*-value
Age (years)	36 (25-49.5)	39 (28-49)	38 (27.7-52.5)	0. 692
WBC*103/ µL	5.1 (4.3-6.9)	6.3 (4.8-7.5)	6 (4.1-8)	0.091
Hb (g/dl)	12.7 (11.5-14.5)	13.5 (12.1-15)	12.7 (11.7-14.5)	0.017
Platelet*103 /µL	211 (166-268)	239 (179-305)	197 (150-252)	0.166
Granulocyte*103 /µL	3 (1.95-3.95)	3.7 (2.6-4.6)	3.2 (2.2-4.47)	0.102
Albumin g/dl	4.1 (3.85-4.5)	4 (3.5-4.1)	3.9 (3.7-4.1)	0.416
AST (iu/l)	36 (26-56)	37 (27-67)	41 (24-63)	0.636
ALT (iu/l)	40.5 (25-74)	47 (33-69)	46.7 (24-83)	0.858
ALK (iu/l)	82 (62-105)	87 (67-104)	87 (67-108)	0.829
TSB (mg/dl)	0.7 (0.5-0.97)	0.6 (0.5-0.9)	0.71 (0.59-1.17)	0.128
INR	1 (1-1.1)	1 (0.9-1.03)	1 (1-1.12)	0.387
Urea (mg/d)l	27 (22-33)	23.5 (20-30)	27.7 (22-34)	0.405
S.cr (mg/dl)	0.7 (0.69-0.81)	0.7 (0.6-0.8)	0.8 (0.7-0.9)	0.278

*Median test
IQR interquartile range (P-value significant at alpha <0.05)
PR: PEG-IFN-alfa-2a or alfa-2b + ribavirin
SOF+PR: Sofosbuvir + peg-IFN-alfa-2a or alfa-2b +ribavirin
SOF/LDV: Sofosbuvir + ledipasvir

HCV genotype 4 was present in 48.5% (n=133) of cases followed by genotype 1a in 22.3% (n=61), genotype 1b in 21.5% (n=59), non-specified genotype 1 subtype in 6.2% (n=17) and genotype 1a/b in 0.4% (n=1), so total subtypes of genotype 1 represented 50.4% (n=138) of

the cases. Genotypes 3 was present in 0.4% (n=1) and genotype 6 was present in 0.7% (n=2).

At the end of treatment, 80% (n=100) of patients responded to SOF/PR regimen; 75.6% (n=59) of patients respond to SOF/LDV; 63% (n=58) of patients respond to PR, which was statically significance (p-value<0.001). The results show that 70.8% (n=51) of patient on SOF/LDV regimen; 61.3% (n=68) of patients on SOF/PR regimen and 48.8% (n=42) of patients on PR achieved SVR, which was statically significance (p-value=0.018) figure (1).

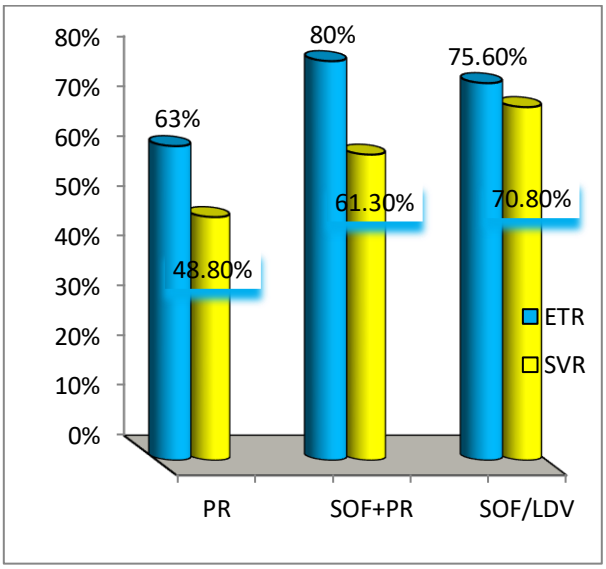

Figure 1: End of treatment response and sustained virological response of three HCV treatment regimens

PR: PEG-IFN-alfa-2a or alfa-2b +ribavirin

SOF+PR: Sofosbuvir+ peg-IFN-alfa-2a or alfa-2b +ribavirin SOF/LDV: Sofosbuvir +ledipasvir

By comparing the responders who achieved SVR to non-responder of all types of treatment, we found that the use of SOF/LDV is associated with a significant response to treatment compared to the other treatment regimens, with more than a three-fold increase in response to treatment (odds ratio = 3.143; 95% CI = (1.591 - 6.208); p=0.001). Genotype 4 is associated with a better response to treatment, with nearly a two-fold increase in response to treatment compared to other genotypes and it was statistically significant (odds ratio = 1.959; 95% CI = (1.079 - 3.558); p=0.001). The most responder genotype to PR was genotype 4 in 53.2% (n=25) of patients affected by G 4 followed by genotype 1a in 46.7% (n=7) of patients affected by genotype 1a, then genotype 1b in 40% (n=6) PR of patients affected by genotype 1b; but these differences were statistically not significance (p-value=0.300). The most responder genotype to SOF/PR was genotype 4 in 68.2% (n=30) of patients affected by genotype 4 followed by genotype 1a in 63.6% (n=14) of patients affected by genotype 1a, then genotype 1b in 50% (n=11) of patients affected by genotype 1b, but these differences were statistically not significance (p-value=0.248). The most responder genotype to SOF/LDV was genotype 4 in 74.2% (n=23) of patients affected by G 4 followed by G 1a in 68.4% (n=13) of patients affected by G 1a, then G 1b at 58.8% (n=10) of patients affected by G 1b, but these differences were statistically not significance (p-value=0.249) figure (2).

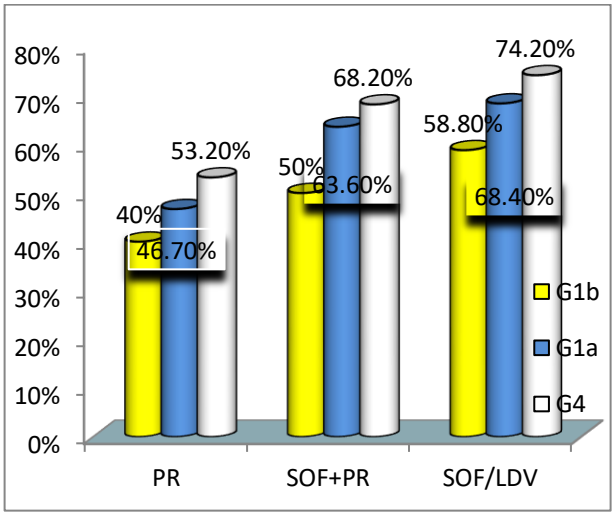

Figure 2: HCV genotype distribution according to SVR

PR: PEG-IFN-alfa-2a or alfa-2b +ribavirin,

SOF+PR: Sofosbuvir+ peg-IFN-alfa-2a or alfa-2b +ribavirin,

SOF/LDV: Sofosbuvir +ledipasvir

Discussion:

Treatment of HCV infection and achieving SVR at which the patient is considered to be cured is a very important issue as it reduces the spread of infection , improves the quality of life and decreases the progression of disease.(4,5) The study aimed to evaluate the efficacy of the three types of treatment of hepatitis C infection in a group of Iraqi patients.

The predominant genotype was genotype 4(48.5%(n=133) followed by genotype1a(22.3%(n=61);genotype 1b(21.5%(n=59));and non- specified genotype 1(6.2%(n=17). This result was similar to the results of Al-Kubaisy et al., (2015) in Iraq , who they reported a predominance of genotype 4 followed by genotype 1a then genotype 1b. (6) Sadeghi et al.,(2016) showed that the genotype 4 was predominant in Saudi Arabia (G4 65%,G123%), Kuwait (G4 43% ;G1 28%) , Qatar (G4 64%;G1 20%) and Egypt (G4 69%; G1 5%),(2). These results are in contrast to those of Khdeir et al., (Basra 2016) which showed that the genotypes 1a and 1b were the predominant genotypes.(7) The regimen with the highest SVR was (SOF/LDV) followed by SOF+PR and then PR. In the SOF/LDV group, ETR

was 75.6% and SVR was 70.8%, which were low in comparison with ION-1 study (2014) which showed 100% SVR for naïve patients infected with genotype 1(8), ION-3 study (2014) showed an ETR of 100% and SVR of 95%.(9) Gutierrez et al., (2015) showed a SVR 95%.(10) The most responder genotype in SOF/LDV was genotype 4 (74.2%) followed by genotype 1a (68.4%) followed by genotype 1b(58.8%).In ion 2 study the most responder genotype was genotype 1a (95%) followed by genotype 1b (87%). (9) While in ION-3 study the most responder genotype was genotype 1b (98%) then genotype 1a (93%).(9) Zenq et al., (2017) showed SVR of generic SOF/LDV to be 96.9% for G 1b infected patients.(12) Bagaglio et al., in 2015 showed that resistance-associated polymorphisms were prevalently detected in sequences from Europe and in particular in G1b isolates, indicating a different NS5A resistant profile according to geographic origin of subtype. (13) While in the USA, the most resistance genotype was genotype 1a which commonly present to elbasvir/ graziprevir.(14) Franciscus in 2014 showed that people with HCV genotype 1 subtype 1a respond more favorably than people with 1b. (15) In case of SOF/PR group; the result of end of treatment was 80% and SVR was 61.1%, while the report of EASL Barcelona 2016 showed that end of treatment (ETR) and sustained viral response rates at week 4 (SVR4) were 99.6% (220/221) and 94.2% (129/137) respectively(16). Neutrino study (2013) showed that ETR of SOF/PR was 99% and SVR (89%) for G1 (92% of genotype 1a and 82% genotype 1b and 97% for genotype 4) (17). Atomic trial (2013) showed SVR 24 for genotype 1 was 88% and for genotype 4 was 82%(18); Proton study (2013) showed that SVR 24 was 91% for genotype 1(19); Elsharkawy et al., (Egypt 2017) showed a 94% SVR.(20) In the present study SVR is much lower; as in G4, the SVR result was 68.2% follow by genotype 1a (63.6%) and then genotype 1b (50%), similar to the results of Neutrino study in respect to the order of response to therapy.(17) In case of PR group in the present study, the result of ETR was (62.4%) and SVR 48.8%, almost similar to the study of Donato et al., in Italy (2013) where ETR was 59% and SVR 46%(21); as well as the study of Moutaz, etal in 2012 where approximately 62.5% of patients had ETR, and 49.6% had SVR(22) and that of Hassan et al,. (Egypt 2015) which showed 51.4% SVR.(23) The most responder genotype to PR was genotype 4 which showed SVR 53.2 %, followed by genotype 1a 46.7% and genotype 1b 40%. The study done by Kamal et al., (2005) (24) in Egypt showed that the ETR was (70%) and SVR 69% for genotype 4 which is higher than the present study (ETR for G4 was 68% and SVR 53.2%). In the present study G1a, ETR was 62.5% and genotype 1b ETR was 58.8% which is similar to the results of Pellicelli et al., (2012) (who showed that G1a ETR and SVR was 65% and 55% respectively; G1b ETR and SVR was 58% and 43% respectively.(25) The PROBE study, a prospective observational multicenter study in Italy, included more than 6000 HCV infected patients, showed that SVR was marginally associated with subtype 1a compared to subtype 1b when treated with PR (OR 1.41; 95% CI 1.0-2.03). (26) While Proton study for genotype 1 showed that SVR 24 was 58%.(27) The International Liver Congress 2016 in Barcelona, Spain, showed high sustained virological response (SVR) after treatment with generic sofosbuvir, ledipasvir, daclatasvir and ribavirin, confirming clinical efficacy equivalent to outcomes seen of branded combination treatments.(16) While such result of generic drugs are not obtained in the present study by use of generic SOF/LDV or generic SOF in SOF+PR which could be due to that sofosbuvir and SOF/LDV used by Iraqi patient were bought by the patients themselves from different sources some of these sources were not under quality control of ministry of health (M.O.H). Presence of resistance of NS5A inhibitors was still possible in our patients as multiple mutations in HCV replicons (genetic units of replication) can cause significant resistance; which was not assessed and can be a cause of low response. Yet in Sofosbuvir, only the single amino acid substitution S282T conferred resistance and decreased the activity of the NS5B inhibitor. This substitution gave a two-fold to 18-fold decrease in susceptibility of the virus to Sofosbuvir. (28)

Conclusions:

Generic SOF/LDV associated with the best response to treatment; which was three times more than PR in achieving SVR and it was statistically significant (Odds ratio = 3.143; 95% CI = (1.591 - 6.208); P=0.001). The most responder genotype in the study group was genotype 4 and the least responder genotype was genotype 1b.

Authors' contribution:

Wasan Khraibet Jasim AL-Saedi :collected samples , wrote the article and made the statistical analysis

Nawal Mehdi Firhan AL-Khalidi: help in sample collection, and gave correction advices about article.

Ahmed Abass Hussein: reviewed the written article and gave correction advices

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المقارنة بين ثلاثة انظمةعلاجية مختلفة في علاج التهاب الكبد الفايروسي سي ل 295 مريض عراقي

د. وسن خريبط جاسم
د. نوال مهدي فرحان الخالدي
د. احمد عباس حسين

الخلاصة:
خلفية البحث: عدوى التهاب الكبد الفايروسي سي هي مشكلة صحية عالمية في جميع انحاء العالم يتم استخدام انظمة علاج مختلفة تنتج معدلات استجابة مختلفة تتأثر بالعديد من العوامل.
الاهداف:تقييم فعالية ثلاثة انظمة علاجية مختلفة في 295 مريض عراقي مصاب بفيروس التهاب الكبد االوبائي سي المزمن .
المرضى والطرق: هي دراسة الاتراب الرصدية حيث تم تسجيل 295(133 من الذكور و162 من الاناث)المصابين بعدوى فيروس التهاب الكبد الوبائي سي المزمن في الفترة مابين اب 2015 الى كانون الثاني 2017 من عيادة امراض الجهاز الهضمي في مستشفى بغداد التعليمي ومستشفى امراض الجهاز الهضمي والكبد التعليمي.تم اجراء قياس نسبة الفايروس والتنميط الجيني لكل مريض وتم متابعة المرضى الذين قدموا للعلاج عن طريق قياس نسبة الفايروس في نهاية العلاج وبعد ثلاثة اشهر من انتهاء العلاج.
النتائج: غالبية المرضى المصابين بفيروس التهاب الكبد الوبائي سي المزمن المحققين استجابة فيروسية مستدامه(تعرف بعدم تحسس الفايروس بعد 12 الى 24 اسبوعا من نهاية العلاج) كانوا من مجموعة النظام العلاجي السوفوسبوفير/ليديباسفير بنسبة 70.8% (51 من 72) وبعده السوفوسبوفير مع البيك انتيرفيرون والريبافرين وبنسبة 61.3% (68 من 111) وبعده البيك انترفيرون والريبافرين بنسبة 48.8% (42 من 86)
الاستنتاجات: الدواء الاكثر فعالية هو السوفسبوفير مع ليدي باسفير وبعده السوفسبوفير مع البيك انتيرفيرون والريبافرين وبعده البيك انتيرفيرون والريبافرين ,وكان النمط الوراثي الاكثر استجابة في المريض العراقي هو التركيب الوراثي 4 وكان النمط الوراثي الاقل استجابة هو التركيب_الوراثي ب1
مفتاح الكلمات: التهاب الكبد الفايروسي سي، سوفسبوفير, انتيرفيرن, ريبافرين

Open Access Original Article

Observational Study of the Multisciplinary team role (MDT) on Healthcare Management of Cancer Patients: Benefits and Barriers, AbuDhabi 2017

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Ibtisam H. Al Obaidi* **FICMS**

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Abstract:

Background: Multidisciplinary team meetings (MDTs) are designed to optimize patient outcomes. It appears intuitive that MDTs are essential to clinical decision-making and patient management; however, it is unclear whether that belief is supported by evidence. With regard to cancer patients, studies demonstrated that treatment plans made by interacting health care professionals are more effective than those made by individual practitioners.

Objectives: To assess the impact of multidisciplinary teams (MDTs) on clinical decision-making and patient outcomes.

Methods: We follow a descriptive questionnaire survey study design and created a (10) sections surveymonkey that was distributed via email to (150) experts in surgical oncology, general surgery, oncology, radiation oncology, pathologists, and administrative staff. Fourty (40) completed responses were collected to ensure a statistical basis on which to draw sound conclusions. The remaining 110 staff have submitted incomplete answers. Answers were discussed in a separate MDT meeting with most of the participants.The survey was followed by an interpretation of the respondents' results and comparison with literatures.

Results: 75% of the participants chose "Agree and strongly agree", supporting the hypothesis that MDT meetings ensure an effective and up-to-date management guidelines. This means that the risk of not discussing a cancer patient cannot be neglected any longer. So the hypothesis statement (H0) is rejected and the alternative statement (Ha) is accepted.

Conclusions: The majority of participants saw the value in the MDT process and expressed support for its implementation locally and nationally; however, feedback about the most appropriate format is yet to be established. The clinicians identified the need for agreed standards in MDT performance.

Keywords: MDT meetings,MDM,MDC multidisciplinary care,cancer care.

Introduction:

MDTs management of cancer patients can result in a more effective treatment plans, MDMs also lead to increased communication between disciplines that are useful for training junior doctors(1). Although MDMs generate many benefits, the meetings do not always lead to optimum decision-making as outcomes have been found to be highly inconsistent and largely dependent on the effective participation of the team members (2,3). Health professionals in attendance could be radiologists, pathologists, medical oncologists, surgeons and supportive care professionals (4). Our aim is to further understand the process, participation and operations of cancer MDT meetings in three private hospitals in Abu Dhabi based on the experience and knowledge of participants. In a longitudinal study with a large cohort of cancer patients, Shulman et al and Slavova et al demonstrated that treatment plans made by interacting health care professionals are more effective than those made by individual practitioners (5,6,7). In addition to more effective treatment plans, Lamb et al, Balasubramanian and Caudron et al found that MDMs also led to increased communication between disciplines that are useful for training junior doctors (8, 27, 28). Shulman et al also found that specialists from one discipline understand the possibilities and constraints of other disciplines when exposed to other disciplines through MDMs.

Prades et al, Soukup et al and Hahlweg et al found that many participants in an MDM setting reported

* *Central Public Health Laboratory CPHL, Ministry of Health, bhazeez@gmail.com*

large amount of time was wasted due to disagreements between participants. However, the same survey revealed that participants were still positive about the outcome of MDMs and believed that it led to better plans for care (9, 24, 26). Although, MDMs are clearly a group decision-making process, few studies have explored MDM processes and outcomes from the perspective of group reasoning. Some participants dominate due to their authority or charisma; not all information may be fully shared. Venod, Pillay et al, Harris et al, Carlson and Soukup et al. found that a lack of proper communication and interpersonal interaction could account for 70–80% of errors in health care (10, 11, 22, 23, 25). As a communication process, an MDM cannot readily be evaluated using the same approach as medical interventions. This view is consistent with that held by Saini et al and Nguyen et al who found that information technologies in health care were often inappropriately evaluated using randomized clinical trial methodologies (12, 29).

Objectives: Our aim was to further understand the process, participation and operations of cancer MDT meetings in three private hospitals in Abu Dhabi based on the experience and knowledge of the participants. Our objective was also to identify obstacles to effective and sustainable MDT meetings, particularly how information and communication with the minimum set of conditions required for effective multidisciplinary case conferencing.

Methods

A questionnaire survey method (study design) used to verify the alternative hypothesis of MDT meetings benefits. The correlational method was mainly used to get a statistical test to find and rate patterns between organizational factors and opinions of decision makers (clinicians) being responsible for patient management.

The survey instrument created using Survey Monkey account on www.surveymonkey.com. This service is very easy to use and an unlimited number of participants can answer. The service is also free of charge. After the survey is finished, the results are made available in a spreadsheet format, which allows analysis, and report generation. The survey was pilot-tested with three users who were not included in the main study to get their feedback on the survey itself (length, clarity, and time to complete). Survey Monkey stored all respondents' data electronically, which was exported to Microsoft Excel for analysis purposes. Respondents were not identified in any way, and the survey was completely anonymous.

Timing and duration: The survey was announced to participants a few days in advance and then the target group received an email with details regarding the survey at the end of June 2017. The survey consisted of 10 questions. The time needed to complete the survey did not exceed 10 minutes. The participants were not involved in the design of the survey.

Survey Participants: The MDM participant were health care professional who had participitated in at least one meeting during the past six months from the date of the survey, and non-MDM participants were those who had not attended any meeting (2). Of the 150 survey respondents, 40 were MDM experienced participants who submitted complete answers as they were regularly attending the MDT meetings. Thus, the results presented are based on the responses of those who were regularly present in the meetings during the past six months prior to answering the survey questionnaire. The selection of experienced participants was very important in order to get high quality results. This process was performed manually to ensure that only cancer experts selected from all three hospitals, were able to participate. The questions within all parts of the questionnaire aimed to gather qualitative as well as quantitative answers. Qualitative method has the advantage that participants can answer quickly since answers are pre-defined and can be selected with one click only. Most answers are based on a Likert-type scale. The applied Likert-scale includes five-level Likert items, from "absolutely disagree" to "absolutely agree" [Tables 1-2] (2). The last part consists of open questions with open text fields, which the participants could use to give additional comments and recommendations on the subject.

Survey Questionnaire:

Section 1: Biography of participants (age, specialty, years of experience and MDT meeting involvement).

Section 2: MDT meetings and the communication patterns used.

Section 3: Follow up activities after MDT meetings (booking investigations and following up results or notifying patients of the meeting recommendations).

Section 4: The communications technology of increasing information can support the physicians' role and reduce the time taken in conducting an MDT.

Section 5: Increasing the amount of information and how communication technology support physicians role to reduce the time taken per patient in the conduct of the meeting.

Section 6: How patient-related data and information are documented during the meeting (written by hand / entered electronically).

Section 7: How much of physicians' time is involved in follow up activities for the meetings attended on average? (less than 30 minutes - 4 hours per meeting.

Section 8: How long is each patient discussed on average.
Section 9: Opportunities to examine the workload on MDT participants when there is an excessive number of patients who require an additional or re-discussion at the MDT meetings (when the right staff were not present or the right information was not available).
Section 10: MDT meetings current practices and the extent to which the clinician concurs with the statements provided.
Answers were measured by a scale from 1-5.

Results

The majority of respondents (75%) agreed about benefits of MDMs being the proper approach to improve cancer care, with only 5% having some form of disagreement. More than two thirds (67.5%) of participants agreed that MDMs are not a waste of time, while 10% think they are a waste of time. The opinion of "Successful MDT meetings are based mostly on the leadership of the meeting" reveals that 67.5% of survey participants felt that the leaders of the meetings were effective in not wasting time during the meetings. Participants noted the high number of staff involved in conducting an MDM and raised the issue of cost effectiveness of these meetings; (72.5%) of respondents agreed with the opinion: "(MDTs) meetings are cost effective" as in (Table 1). An analysis of answers to the question (How long is the average time for each case discussion?) is shown in (Figure 1). The answers illustrate that most cases are only discussed for around 5-10 minutes, and that rarely is a case discussion last for more than 30 minutes. Participants' opinions on the time required to document the discussion being either during or after the MDMs, are shown in (Table 2). Minimal usage of direct entry into electronic devices for documentation in was agreed by 15% of resondents compared to 70% prefering manual data recording.

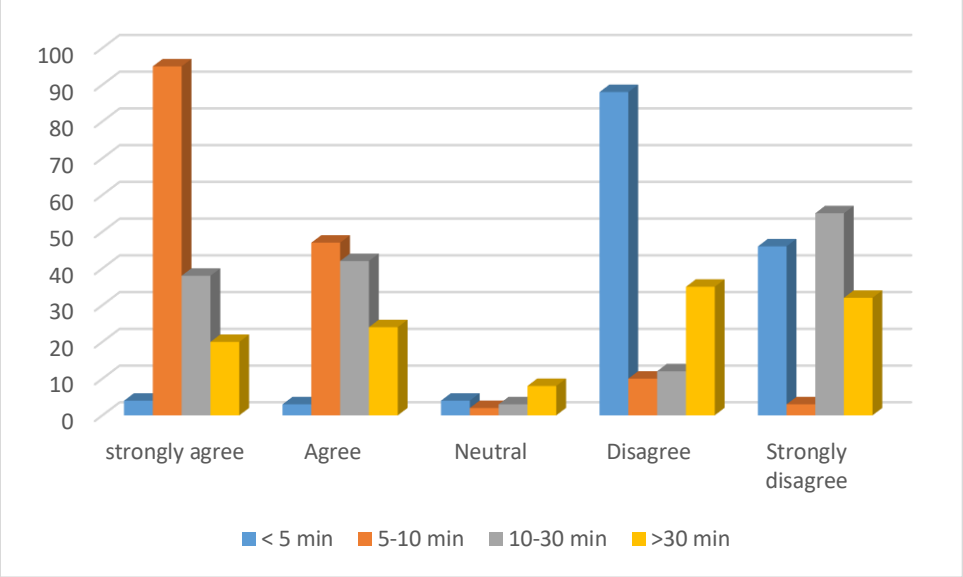

Figure 1. Average time allocated for each case discussion, majority of responces agree on 5-10 minutes

Table 1. Participants' opinions on MDMs impact on the standard of cancer care

Participants' opinions (N=40)	Strongly disagreed No. (%)	Disagree No. (%)	Neutral No. (%)	Agree No. (%)	Strongly Agree No. (%)	Skipped No. (%)
MDTs improve the quality of care	1 (2.5)	1 (2.5)	5 (12.5)	3 (7.5)	27 (67.5)	3 (7.5)
I do not believe MDTs are a passing fad	1 (2.5)	3 (7.5)	4 (10.0)	7 (17.5)	20 (50.0)	5 (12.5)
MDTs are cost effective	2 (5.0)	3 (7.5)	4 (10.0)	9 (22.5)	20 (50.0)	2 (5.0)

Table 2: Participants' opinions on time duration required in MDM documentation

Participants' opinions (N=40)	Strongly disagreed No. (%)	Disagree No. (%)	Neutral No. (%)	Agree No. (%)	Strongly Agree No. (%)	Skipped No. (%)
Long time to document all the relevant case data DURING the meeting	8 (20.0)	20 (50.0)	5 (12.5)	4 (10.0)	2 (5.0)	1 (2.5)
Long time to document all the relevant case data AFTER meeting	2 (5.0)	20 (50.0)	11 (27.5)	5 (12.5)	1 (2.5)	1 (2.5)

Statistical Analysis:
using Chi-square test for agreement among clinicians on the value of MDT, where hypothesis is: H0: MDT meetings have no impact on cancer patients management. Ha: MDT meetings have an impact on cancer patients management.

Computation of the expected frequency counts, the Chi-square (X^2) statistics and the degree of freedom (DF). The result reveals a P-value < 0.05, which means we have to reject the null hypothesis (H0) and accept the alternative hypothesis (Ha) to conclude that there is an acceptable level of agreement on MDTs impact.

Discussion:
Responding clinicians noted the beneficial added value of the MDM approach to their work and management. Participants' opinions on MDMs role in upgrading the standard of cancer care was supportive in 75% of participants. One answer mentioned "(MDMs) are very informative and educational, giving a greater understanding of pathology and its impact on treatment options". There were various reasons mentioned as to why MDMs were possibly not as effective or efficient as they could be. A frequent remark about the workload when too many cases were being discussed at a meeting, and enough time was not given to any one case treatment plan. Our results show that most patients are only discussed for about 5-10 minutes, and that rarely a case can be discussed for more than half an hour. This is not inconsistent with the observation that there is no enough time allocated to discuss the plan for patient treatment. However, this finding would suggest that MDMs are not seen as inefficient. Some may have the belief that MDMs are a waste of time, and do not need to be taken seriously, but it is clear from the results that this was not true for the majority of the participants. Despite some negative feedback, most of the objective data collected indicate a strong support in the potential utility of MDMs (14, 15, 30, 31). As one participant claimed "The MDMs often lead to delay in decision making, even though an incorrect decision is less often made". It is clear that participants would like to observe the scientific guidelines that proves the outcome of MDMs and view a reduction in inefficiencies that have been noted (13, 16, 32, 33). Cost effectiveness of these meetings are confirmed by 72% of respondents (agreed or strongly agreed) that (MDTs are cost effective). Some feedback indicated that many MDMs become side talks and that time should be more effectively allocated for actually examining patients face-to-face. There was a little difference in the responses on whether a long time is required to document all the relevant case data DURING the meeting or AFTER the meeting with more responses favoring documentation during the meeting. Review of literatures reveals that our observations were in parallel with regards to MDT workload. Haward et al. (17) described a systematic assesment of the effectiveness of breast cancer team. The researchers evaluated the workload, team organization and working methods. Workload was defined as "new cancer annual caseload of the team related to the actual time committed by each breast team member" (17). It was found that team workload predicted the clinical effectiveness of the team positively. Their results also reinforced British guidelines that sufficient workload is required for viability and effectiveness of breast cancer teams. Nouraei et al (18) studied the increase of the efficiency of the MDT process in the head and neck tumour cases at Charing Cross Hospital in England. After conducting a systems analysis of this process, the researchers renewed the process and created a new data management solution to implement the process. Efficiency on-the-whole was improved by 60% as found from follow-up evaluation of the process. Kane et al (19) studied work processes and determined time demands for radiologists and pathologists at a hospital in Ireland. Their method addressed the documentation and analysis of all work connected with MDMs involving pathology and radiology in a particular month. Results of their study included:

- "Time spent at meetings, and in preparation for MDT meetings is significant"
- "The exchange of patient materials with outside institutions is a cause for concern when full data are not made available in a timely fashion."

The most recent and most closely related work to our study is that of Pillay et al (11). There was limited evidence for improved survival outcomes of patients discussed at MDT meetings. Between 4% and 45% of

patients discussed at MDT meetings experienced changes in diagnostic reports following the meeting. Patients discussed at MDT meetings were more likely to receive more accurate and complete pre-operative staging, and neo-adjuvant/ adjuvant treatment. The conclusion from this study highlighted the impact of MDT meetings on patients' assessment and management practices. However, there was little evidence indicating that MDT meetings resulted in an improvements of patient survival. This also supports our reslts of 75% of respondents agreeing on the benefits of MDMs and the proper approach to improve cancer care rather than survival (20, 21). Our literature review shows that MDT meetings are important to clinical decision-making and patient management [Croke and El-Sayed 2012] (4) because they provide an opportunity for health care professionals to review cases, re-evaluate radiology and pathology reports, and discuss various treatment options (4). There is also strong evidence to show that MDT significantly influence clinical decision-making, and it is not a waste of time. This was consistent with our findings that 68% of opinions do believe the same.

Conclusion:

There is a recognized and well-supported growing value of MDTs in the clinical decision-making that lead to changes in diagnoses and physician management decisions. However, no strong evidence to support the opinion that they improve patient outcomes.

Recommendations:

A well-designed prospective study has to be carried out to provide proof of principle (Value of MDTs). MDTs is a peer review of cancer cases that is feasible and acceptable to recognize further development and to refere to a national benchmarking of MDTs against established outcome measures is required if this process is to be widely implemented. Concerns expressed by participants highlight the need for systematic quality improvement (QI) processes such as the peer-review process to be endorsed at a jurisdictional and executive level, and for there to be a commitment to provide teams with the appropriate resources and support necessary to conduct the MDT reviews and implement relevant recommendations. If peer review is adopted, a process for monitoring the implementation of recommendations needs to be established, otherwise uptake may be limited. It would be of great interest to further study this new model implemented in our medical institute, as in Baghdad Medical city by undertaking more observations from the team, whether through surveys, interviews, or task force groups. Further study would enable support of additional improvements to the multi-disciplinary team meeting model, so as to establish universal effectiveness in the goal of caring for patients with cancer.

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دور الفريق متعدد التخصصات في ادارة الرعاية الصحية لمرضى السرطان في ثلاث مستشفيات في ابو ظبي , الفوائد والمعوقات

د. ابتسام حسين العبيدي

الخلاصة

خلفية البحث: ان اجتماعات الفريق الطبي متعدد التخصصات تهدف لتحسين نتائج علاج مرضى الاورام. وتعتبر هذه الاجتماعات اساسية لغرض اتخاذ القرار الطبي في رعاية هؤلاء المرضى . وبالرغم من ذلك, فانه من غير الواضح ما اذا كان هذا الرأي يستند الى دليل علمي. ان خطط علاج امراض السرطان التي يتبناها مجموعة من اخصائيي الرعاية الصحية تكون اكثر فاعلية بالمقارنة بخطط العلاج التي يتخذها الطبيب بمفرده.

الاهداف: ان الهدف من هذه الدراسة هو تقييم الفرضية القائلة باهمية اجتماعات الفريق المتعدد التخصصات في ثلاث مستشفيات في ابوظبي لعام 2017 وتأثير ذلك على قرار العلاج السريري وحالة المريض. ان اجتماعات الفريق متعدد التخصصات المكون من فريق طبي وفريق ساند من ذوي الخبرة , والذي يأخذ بنظر الاعتبار اساسيات خطة العلاج بعد الاتفاق على التشخيص, ومستقبل المرض بعد علاجه, اضافة لاتخاذ القرارات المشتركة بهذا الخصوص والتي تعتبر افضل من اتخاذ قرار التشخيص والعلاج الذي يتبناه الطبيب المعالج بمفرده.

طرائق البحث: تم وضع فرضية ان اجتماعات الفريق المتعدد التخصصات بامكانها خفض نسبة الوفاة وتحسين نوعية حياة مرضى السرطان. وتم وضع التساؤل اما برفض هذه الفرضية باعتبار النتائج السلبية المترتبة على اجتماعات الفريق متعدد التخصصات , او بقبول الفرضية والتي تعتمد على الفوائد المترتبة على اجتماعات الفريق متعدد التخصصات. وقد تضمن البحث توزيع المسح الالكتروني والمكون من عشرة اجزاء وارسل عن طريق البريد الالكتروني لمجموعة مختارة من الاطباء الاختصاص والاختصاص الدقيق في جراحة الاورام والجراحة العامة, علاج الاورام, واختصاص الاورام الاشعاعي, اطباء النسيج المرضي (الهستوباثولوجي) والاشعة التشخيصية اضافة لمشاركة الفريق الاداري .تم اعتماد 40 اجابة للمسح الالكتروني لغرض تجنب الانحياز الاحصائي وللوصول الى نتائج دقيقة بعد تنقسيرها ومقارنتها بنتائج البحوث المنشورة مسبقا في نفس الموضوع.

النتائج: اظهرت النتائج ان اكثر اجابات المسح الالكتروني قوة وثبات جاءت من المشاركين الذين يعتقدون باهمية اجتماعات الفريق متعدد التخصصات بالرغم من المعوقات الآنية. كانت كل الاجابات متفقة وتدعم فرضية ان اجتماعات فريق متعدد التخصصات لها تأثير مباشر على علاج مرضى السرطان. ان نسبة 69% من المشاركين قد اختارت الاجابة " اتفق بقوة" لدعم فرضية ان الفريق متعدد التخصصات يضمن العلاج الفعّال والحديث وفقا لقواعد العلاج الارشادية العالمية. ان معنى ذلك ان الخطر الناجم عن عدم مناقشة حالة مريض السرطان لايمكن التغاضي عنه او اهماله. وبناءاً على ذلك , فقد تم رفض الفرضية القائلة بعدم جدوى من اجتماعات الفريق متعدد التخصصات وتم قبول الفرضية البديلة القائلة باهمية هذه الاجتماعات.

الاستنتاج: ان الغالبية العظمى من المشاركين في المسح يؤيدون اهمية عقد اجتماعات الفريق متعدد التخصصات وعبروّا عن دعمهم تنفيذ عقد الاجتماعات على نطاق المستشفى والمستشفيات الاخرى في عموم البلاد. على الرغم من ذلك, هناك بعض المشاركين اقترحوا في اجاباتهم ان الهيكلية المناسبة لهذه الاجتماعات لازالت غير مثبتّة. تمّ اتفاق هؤلاء المشاركين على الحاجة لوضع اسس يتم الاتفاق عليها لغرض ضمان الاداء والوصول للفائدة المرجوة من اجتماعات الفريق متعدد التخصصات.

الكلمات الدالة: الفريق متعدد التخصصات, اجتماعات الفريق متعدد التخصصات, رعاية السرطان .

Open Access Original Article

Comparison between Mammography and Breast Ultrasound in the Detection of Breast Cancer in Dense Breast Tissue among a Sample of Iraqi Women

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Hiba M. AbdulWahid* **CABMS**

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Abstract:

Background: Breast cancer is the most common cancer reported in women worldwide. In Iraq, it is the most common registered malignancy. Mammography plays a major role in the early detection of breast cancers. Dense breast parenchyma has been reported to be the most important inherent factor that limits depiction of breast cancer on mammogram, and often needs supplementary breast ultrasound for complete assessment.

Objectives: To evaluate and compare the diagnostic performance of mammography and ultrasound in the detection of breast cancer in dense breast tissue.

Patients and methods: A record review study was performed in the Oncology Teaching Hospital/ Medical City from April 2018 to December 2018. The study included forty five females, who attended the Main Referral Center for Early Detection of Breast Tumors during 2017 and 2018 were diagnosed with breast cancer histopathologically. They had dense breast tissues on mammography (either heterogeneously dense breast tissue i.e. category C or extremely dense breast tissue i.e. category D). All patients underwent subsequent breast ultrasound .Their information including the mammogram findings, breast ultrasound, fine needle aspiration (FNA) and biopsy results were reviewed analyzed and compared**.**

Results: Twenty four patients (53.3%) had heterogeneously dense breast tissue (ACR category C) and 21 patients (46.6%) had extremely dense breast tissue (ACR category D). The mammogram detected 36 from 45 breast cancers (80%) while 9 (20%) were not detected by mammogram, so the mammogram had a detection rate of breast cancer of 80% in mammographically dense breast, while breast ultrasound had higher detection rate of about 97.7%. The sensitivity of mammography in extremely dense breast tissue was about 71% and in heterogeneously dense breast was about 87% while ultrasound had shown a higher sensitivity with increasing tissue density (98% vs. 100%).

Conclusion: Breast cancer can be easily obscured and missed in mammographically dense breast tissue due to overlapping surrounding fibroglandular tissue and additional complementary breast ultrasound is highly recommended for a thorough evaluation and to depict mammographically occult breast carcinoma.

Keywords: mammography**,** ultrasound, dense breast tissue, obscured breast cancer.

Introduction:

Breast cancer is the most common cancer reported in women worldwide, accounting for 16% of all female malignancies (1, 2). Previous studies from Iraq have reported that breast cancer is the most common registered malignancy (3) and most of the cases are often reported in middle aged women (4).Mammography plays a major role in the early detection of breast cancers, detecting about 75% of cancers at least a year before they can become symptomatic (5,6). Missed breast cancers on mammogram may be attributed to several factors which include dense breast parenchyma that may obscures a small lesion, poor patient positioning or improper technique, misinterpretation of a suspicious breast lesion as benign , errors of perception , gradual growth of a lesion, and subtle features of malignancy (7). Dense breast parenchyma has been reported to be the most important inherent factor that limit depiction of breast cancer on mammography, and often needs supplementary breast ultrasound for complete assessment (8).Furthermore, dense breast tissues by itself is associated with increased risk of breast malignancy and also reduces the sensitivity of mammogram in cancer detection to as low as 30-48% (9). Breast density is the relative amounts of glandular tissue and fat in the breast and it ranges from nearly completely fatty tissue to nearly completely fibroglandular tissue, which affects the appearance of the breast on mammograms. The American College of Radiology (ACR) -Breast Imaging Reporting and Data System (BI-RADS) Atlas had classified breast density

* *National Cancer Research Center, University of Baghdad. Email: dr.hiba.mohammed85@Gmail.com*

into four categories (7). Breast tissue that is almost entirely fatty is classified as category A, scattered fibroglandular tissue classified as category B, heterogeneously dense breast tissue as category C and extremely dense breast tissue as category D.

Patients and Methods:

A retrospective record review was performed in the Oncology Teaching Hospital/ Medical City in Baghdad from April 2018 to December 2018. The study included forty five females, who attended the Main Referral Center for Early Detection of Breast Tumors during 2017 and 2018 and diagnosed with breast cancer histopathologically. They had dense breast tissue on mammogram (either heterogeneously dense i.e. category C or extremely dense breast tissue i.e. category D).Their information including the mammogram findings, breast ultrasound, FNA and biopsy results were reviewed analyzed and compared.

All mammogram were performed using the Analoge mammogram-Seimens.Two mammographic views were taken; craniocaudal and mediolateral oblique views. The mammographic images were analyzed by a specialist radiologist. The mammographic findings are recorded according to the BIRADS lexicon and include: Any detectable breast mass and its morphology(shape, margin, density, site),microcalcifications (grouped , scattered, regional,…) , an architectural distortion ,skin thickening , nipple retraction ,etc.….

The mammogram findings of those patients were either: No detectable abnormality because the breast density obscured it and further evaluation is needed, focal asymmetry, findings that were suspicious for malignancy such as architectural distortion, grouped microcalcification, etc.… and mammographic findings that are highly suggestive of malignancy i.e. an irregular radiodense mass. Complementary breast ultrasound was done for all patients by a specialist radiologist. The ultrasound findings were subsequently performed and the findings were classified. Ultrasound–guided FNA had been performed for all patients and then biopsied .The corresponding cytological and histopathological results were registered.

Inclusion criteria:

Women aging 35 years old and older with dense breast tissue (category C and D) were included.

Exclusion criteria:

Women on hormone replacement therapy.
Lactating and pregnant women.
Postoperative cases.

Statistical analysis:

The collected data were tabulated and analyzed using Microsoft Excel 2010.The categorical data were presented as frequency and percentage tables.

Results

Forty five female patients with dense breast tissue (ACR breast density category C or D) and with histopathologically proven breast cancer were included. All patients had breast ultrasound and mammogram. Twenty four patients (53.3%) had heterogeneously dense breast tissue (ACR category C) and 21 patients (46.6%) had extremely dense breast tissue (ACR category D). The mean age of the patients was 44.5 years, ranging from (35 to 62 years). The mammogram detected 36 out of 45 breast cancers (80%) while 9 (20%) were not detected by mammogram. Of these nine patients, 6 had extremely dense breast (category D) and 3 had heterogeneously dense breast tissue (category C). No mammographic abnormality was detected in seven of 9 cases. The other two cases appeared as an area of focal asymmetry on mammogram. All these overlooked breast cancers on mammography were detected by subsequent ultrasound examination, which revealed features suggestive of malignancy (BI-RADS IV & V) and all proved to be malignant by subsequent histopathological study. The characteristics of breast cancer not depicted by mammogram are summarized in table 1.

Table 1: The characteristics of breast cancer cases not detected by mammogram

cases	Age (Years)	BI-RADS density	Mammography findings	Maximal Tumor size by US (mm)	US BI-RADS
1	41	D	focal asymmetry	8	BIRADS IV
2	38	D	No detectable abnormality	15	BIRADS V
3	55	C	No detectable abnormality	18	BIRADS V
4	40	C	No detectable abnormality	9	BIRADS IV
5	45	C	focal asymmetry	10	BIRADS IV
6	35	D	No detectable abnormality	13	BIRADS V
7	43	D	No detectable abnormality	14	BIRADS V
8	36	D	No detectable abnormality	16	BIRADS V
9	52	D	No detectable abnormality	10	BIRADS V

The 36 detected breast cancer on mammogram (80%); appeared as an irregular radiodense mass in 13 cases (28.8%), a radiodense mass with partially obscured margin in 11 cases (24.4%), grouped malignant appearing microcalcifications in 5 cases (11.1%), grouped microcalcifications with architectural distortion in 4 cases (8.88%), only architectural distortion in one case (2.2%), and a thickened skin with edematous breast tissue in two cases (4.44%). Malignant features were detected in breast ultrasound of all of these cases except one which appeared on mammography as an area of architectural distortion.

Table 2: Appearance of detected breast cancer on mammography

Mammographic findings	NO.	Percentage*
Irregular spiculated radiodense mass	13	13/45 (28.8%)
radiodense mass with partially obscured margin	11	11/45 (24.4%)
Grouped microcalcification +architectural distortion	4	4/45 (8.88%)
Grouped microcalcification	5	5/45 (11.1%)
Architectural distortion	1	1/45 (2.2%)
Thickened skin with edematous breast parenchyma	2	2/45 (4.44%)
TOTAL	36	36/45 (80%)

*** Calculated out of a total of 45 cases**

In this study, mammography had a detection rate of breast cancer of 80% in mammographically dense breast, while breast ultrasound had the higher detection rate of about 97.7%.Similarly, the sensitivity of breast ultrasound in heterogeneously dense breast and extremely dense breast was found to be higher than mammography. In the current study ,the sensitivity of mammography in extremely dense breast tissue was about 71% and in heterogeneously dense breast was about 87% while ultrasound had shown a higher sensitivity with increasing tissue density (98% VS 100%). Sensitivity was measured based on histopathological results as the gold standard.

Discussion

Previous studies evidence revealed that mammography can depict breast malignancy early in apparently healthy women aging 50 to70 years and subsequently decreasing the mortality rates from breast cancer. Mammography, however, is not so perfect to depict all breast cancers and may miss some cancers in certain cases, particularly in dense breasts. In those women with dense breasts, the normal breast parenchyma and the tumor are difficult to differentiate from each other mammographically. For this reason, some supposed that the addition of ultrasound for those women along with the mammography will detect these tumors that are obscured and missed by mammography alone (10).

In the current study, 24 patients (53.3%) had heterogeneously dense breast tissue (ACR category C) and 21 patients (46.6%) had extremely dense breast tissue (ACR category D). The mammogram detected 36 out of 45 breast cancer cases, missing 9 cases, so the detection rate of the mammogram in this study was 80%.This was in agreement with the study of Okello J. et al in which mammograms detected about 16 out of 22 breast cancer cases, missing six cases, with the detection rate of mammogram of 73% (11). Breast ultrasound had a higher detection rate of about 97.7% in dense breast tissue in this study.

Similarly, this study showed that the sensitivity of mammogram in heterogeneously dense breast was 87% and in extremely dense breast tissue was 71% ,i.e. ; decreasing mammographic sensitivity with increasing breast density ,while ultrasound had a higher sensitivity with increasing tissue density (98% in heterogeneous dense breast VS 100% in extremely dense breast) . These results were in accordance with those of Disha et. al. and many other previous studies (12-15).

Two cases of breast cancer which appeared on mammogram as focal asymmetry (i.e. no typical malignant features were present), the ultrasound had showed an ill-defined hypoechoic area at corresponding region (US BIRADS IV) and subsequently proved to be malignant histopathologically. This was in agreement with what was reported by Samarder et.al. in that focal asymmetrical breast density although is repeatedly seen at mammography and usually due to overlapping fibroglandular tissue but sometimes it is due to a hidden malignancy (16).

All obscured breast cancer cases on mammogram in this study were less than 20 mm in maximal diameter when subsequently evaluated by ultrasound and these represent early stage of breast cancer which expected to have favorable prognosis .These findings were in accordance with what was reported by Okello et.al (11).

Conclusion:

Breast cancer can be easily obscured and missed in mammographically dense breast tissue due to overlapping surrounding fibroglandular tissue. Additional complementary breast ultrasound is highly recommended for a thorough evaluation and to depict mammographically occult breast carcinoma.

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مقارنة بين فحص الثدي بالاشعة السينية (الماموكرافي) والفحص بالموجات فوق الصوتية(سونار الثدي) في كشف سرطان الثدي في نسيج الثدي ذو الكثافة العالية وسط عينة من النساء العراقيات)

م.د.هبة محمد عبد الواحد

الخلاصة:

خلفية البحث : يعد سرطان الثدي من اكثر السرطانات شيوعا في النساء في العالم ، وهو سرطان الثدي هو اكثر السرطانات المسجلة في العراق. يلعب فحص الثدي بالاشعة السينية (الماموكرافي) دور اساسي في الكشف المبكر عن سرطان الثدي. ويعد نسيج الثدي الكثيف من اهم العوامل المتاصلة التي تحد من كشف وتحري سرطان الثدي بواسطة اشعة الماموكرام وغالبا ما يحتاج لفحص الثدي بالموجات فوق الصوتية (السونار) لاكمال تقييم الحالة.اضافة الى ذلك, نسيج الثدي الغدي الكثيف بحد ذاته مصحوب بزيادة خطر الاصابة بسرطان الثدي ويقلل من حساسية الماموكرام في اكتشاف السرطان.

هدف الدراسة: لتقييم ومقارنة الاداء التشخيصي للاشعة السينية (الماموكرام) والموجات فوق الصوتية (سونار الثدي) في اكتشاف السرطان في نسيج الثدي الكثيف.

المرضى وطرق العمل: دراسة مراجعة للملفات تمت في مستشفى الاورام التعليمي في مجمع مدينة الطب في بغداد للفترة من نيسان 2018 الى كانون الاول 2018. شملت الدراسة 45 مريضة ممن راجعوا المركز المرجعي الرئيسي للكشف المبكر عن اورام الثدي خلال 2017 و 2018 وتم تشخيصهن بسرطان الثدي بواسطة الفحص النسيجي. كان نسيج الثدي لهؤلاء المريضات ذو كثافة عالية وهو اما نسيج كثيف عير متجانس (مجموعة C) او نسيج كثيف جدا (مجموعة D). فحص الثدي بالسونار أجري لكل المريضات . تمت مراجعة معلومات المريضات واضباراتهن فيما يخص نتائج اشعة الماموكرام وسونار الثدي ونتائج السحب بالابرة (FNA) ونتائج الخزعة تمت مراجعتها وتم تحليل النتائج وتسجيلها.

النتائج:تمت دراسة خمسة واربعون مريضة ذات نسيج ثدي كثيف ومشخصة بسرطان الثدي. وجد أن 24 مريضة (53.3%) لديهن نسيج ثدي كثيف غير متجانس (مجموعة C) و21 مريضة (46.6%) لديعهن نسيج ثدي كثيف جدا.اشعة الماموكرام اكتشفت 36 حالة سرطان ثدي من بين 45 حالة (80%) بينما 9 حالات مرت غير مكتشفة بأشعة الماموكرام(20%) فتكون نسبة اكتشاف سرطان الثدي بواسطة أشعة الماموكرام (80%) في نسيج الثدي الكثيف. بينما فحص الثدي بالسونار لديه نسبة اكتشاف اعلى حوالي(97.7%). كانت حساسيةالاشعة السينية (الماموكرام)في نسيج الثدي الكثيف جدا 71% وفي نسيج الثدي الكثيف غير المتجانس 87% بينما تزيد حساسية الموجات فوق الصوتية لاكتشاف الورم مع زيادة كثافة النسيج الغدي للثدي.(98% للنسيج الكثيف غير المتجانس و 100% للنسيج الكثيف جدا).

الاستنتاجات: سرطان الثدي ممكن ان يمر غير مشخص في اشعة الماموكرام للنسيج الغدي الكثيف بسبب تراكب وتداخل النسيج الغدي للثدي وسونار الثدي المكمل مطلوب في هذه الحالات لتقييم الحالة تفصيليا ولوصف واكتشاف سرطان الثدي العابر غير المشخص بأشعة الماموكرام .

الكلمات المفتاحية: اشعة الثدي(الماموكلافي),فحص بالموجات فوق الصوتية ,نسيج ذو كثافة عالية, سرطان الثدي المستتر

Open Access Original Article

Role of Two- Dimensional Speckle Tracking Strain versus Conventional Echocardiography in the Assessments of Left Ventricular Systolic Function in Middle-aged Hypertensive Patients.

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Mahasen M. Abd Al-Majeed * **MBChB, DDV, MSc**
Najeeb H. Mohammed** **MBChB, DM, MSc, PhD**
Ghazi F. Haji*** **FICMS**

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Abstract:

Background: Global longitudinal strain (GLS) echocardiography is a new technique that can be used to detect an early left ventricular dysfunction in various heart diseases. Systemic hypertension is a major risk factor for cardiovascular accidents. The early managementof its complication on the heart plays an important role in the outcome of the disease. Hypertension is associated with changes in several aspects of left ventricular structure, function, and systolic strains. Various echocardiographic techniques are used to evaluate left ventricular function in hypertensive patients.

Objectives: To evaluate the effectiveness of speckle tracking global left ventricular strain percentage (GLVS%)in the assessments of left ventricular systolic function in comparison to conventional echocardiography in middle-aged hypertensive patients.

Patients and Methods: The study was conducted from December 2017 till November 2018 at the Department of Echocardiography and Catheterization / Baghdad Teaching Hospital – Medical City, Baghdad, Iraq. One hundred and four hypertensive patients classified as; group I that involved patients with reversed E/A ratio on PW Doppler with reversed Pulsed Wave (PW) tissue Doppler study and group II with patients having normal E/A ratio on PW Doppler and reversed E prime/A prime on PW tissue Doppler study. The control (group III) recruited from the relative of the patients included 104 sex and age-matched healthy individuals. A detailed history with the recommended investigations and blood pressure measurements was performed for all participants. Additionally, echocardiography examination was implemented using standard methods, considering left ventricle (LV) internal dimension, LV ejection fraction percentage (LV EF%), LV diastolic function using PW Doppler and lateral mitral annular tissue Doppler, S prime, Mitral annular plane systolic excursion (MAPSE) and global LV speckle tracking strain percentage (GLVS%).

Results: Group I included 76 patients with a mean age of (48 ± 6.6 years) and group II included 28 patients with a mean age of (48 ± 6.6 years**).** All the participants had normal EF%(> 60%), MAPSE (> 13 mm), and S prime (>9 cm /sec) while there were a significantly decreased GLVS% in the diseased groups in comparison to the control one ($P < 0.005$) being less in group II (-14 ± 1%) than in Group I (-16 ± 1%). In addition to a significant negative linear correlation between GLVS% with that of pulse pressure and IVST respectively (p=0.04) and with that of E/A ratio and E/E prime ratio (p=0.001).

Conclusions: GLVS% is a better method in the assessment of LV systolic function in in middle-aged hypertensive patients than conventional echo methods since it could detect an early impairment in LV systolic function despite preserved LV systolic function measured by the conventional echo methods.

Keywords: Systemic hypertension; Tissue Doppler Imaging; Speckle tracking echocardiography.

Introduction:

Hypertension is a major risk factor for cardiovascular diseases with high morbidity and mortality as it increases the heart work (1,2).

** Dept. of Physiology, College of Medicine, AL-Iraqia University.* Correspondence email: Mahasen_Abdulmajeed@aliraqia.edu.iq
***Dept. of Physiology, College of Medicine, University of Baghdad. Dr._najeebalmously@yahoo.com*
****Dept. of Medicine, College of Medicine, University of Baghdad. Ghazi_haji@comed.uobaghdad.edu.iq*

Systemic pressure overload causes different changes in longitudinal, radial and circumferential mechanics of the heart (3). In addition to mechanical changes, systolic and diastolic functions are significantly affected in patients with systemic hypertension (4).

Echocardiography is a non-invasive most widely used diagnostic test in cardiology, which is also safe and accurate in the diagnosis of cardiac diseases in all ages even in pregnant and fetal life (1, 5). Although echocardiography is a second-line study in the evaluation of hypertensive patients, it is a valuable, easily reproducible tool to give clue impression about

LV geometry, systolic and diastolic changes. Left ventricular ejection fraction percentage (LV EF%) represents the global result of both longitudinal and circumferential contraction; it provides only an indirect estimate of myocardial contractile function and does not measure it directly. Second, it is readily influenced by a number of factors including loading conditions, heart rate, etc. Third, and the most important, it is not sensitive enough to detect subtle changes in the contractile function and therefore not suitable for detecting subclinical myocardial damage (1). Mitral annular plane systolic excursion (MAPSE) has been suggested as a parameter for left ventricular (LV) systolic function which reflects LV longitudinal function and thus provides complementary information to EF%. Moreover, reduced MAPSE could be used as a sensitive early marker of LV systolic dysfunction in hypertensive patients with normal EF, where compensatory increased circumferential deformation might mask the reduced longitudinal deformation (6).

In Tissue Doppler Imaging (TDI) the S prime velocity waveforms which correspond to the peak systolic contraction velocity correlates well with global LV function even though it is very much preload-dependent (7). Echocardiographic strain imaging is an innovative approach recently developed for the assessment of LV myocardial mechanics, an angle-independent technique, because it tracks deformation between acoustic markers in the ultrasonic image in two dimensions and employs automated algorithms to analyze temporal variations (frame to frame) in the mobility of acoustic speckle markers of 20-40 pixels' size along different spatial orientations. Strain is the percentage change in the length of a myocardial segment during a given period of time and has a unit of %. As the myocardium shortens during systole, the strain has a negative value but when there is stretch or lengthening of the myocardium, the strain becomes positive. The gray-scale image on echocardiography is composed of several bright speckles that are produced as a result of the scatter of the ultrasound beam by the tissue. The STE software identifies these speckles and then tracks them frame-by-frame using a 'sum-of-the absolute ifferences' algorithm. From this data, the software automatically resolves the magnitude of myocardial deformation in different directions and generates strain (8, 9). This study aimed to Correlate the effectiveness of speckle tracking echocardiography using global left ventricular strain percentage (GLVS%) with the conventional echocardiography in the assessments of LV systolic function in middle-aged hypertensive patients.

Patients and Methods:

This study was performed from December 2017 till November 2018 at the Department of Echocardiography and Catheterization / Baghdad Teaching Hospital – Medical City, Baghdad, Iraq. One hundred and four patients with essential(primary) hypertension with an age range from 35 to 55 years of both sexes were included. These patients were categorized into two groups; group I patients on Pulsed Wave Doppler (PWD) with reversed E/A ratio and reversed Eprime/Aprime ratio on PW tissue Doppler image (TDI), and group II patients with normal E/A ratio on PWD and reversed Eprime / Aprime ratio on PW by TDI. One hundred and four sex and age-matched healthy individuals were recruited from the relative of the patients as a control group III. Patients with ischemic heart disease, diabetes mellitus, renal failure, primary pulmonary disease, valvular heart diseases, thyroid diseases, hyperlipidemia, SLE, atrial fibrillation, obesity, cardiomyopathy, infiltrative cardiac disease, current and history of heavy smoking and those with poor quality echocardiographic images were excluded. All individuals received written information and gave informed consent.

Medical history, ECG, CXR, investigations that are required to exclude the diseases in the exclusion criteria were done. Measurements and calculation of BMI and BSA. Blood pressure were taken according to the American College of Cardiology (ACC) and American Heart Association (AHA) guideline for blood pressure measurements (10) using Rossmax MG150f Digital sphygmomanometer.

Echocardiography was done including standard 2-D and Doppler studies according to standardized protocol of American Society of Echocardiography (ASE) and the European Association of Echocardiography recommendations 2015 using a 3.5 MHz transducer with available equipment (Philips CX 50 ultrasound, USA machine). The Inter-ventricular septum (IVSd) and left ventricle posterior wall measurements were calculated from the standard left parasternal long axis view at the end of diastole. Left ventricle (LV) internal dimension during systole and diastole were carefully obtained in the 2D-guided M-mode echocardiography then according to the Teichholz M-mode formula the LV ejection fraction % was calculated by the machine software as shown in figure 1(11, 12).

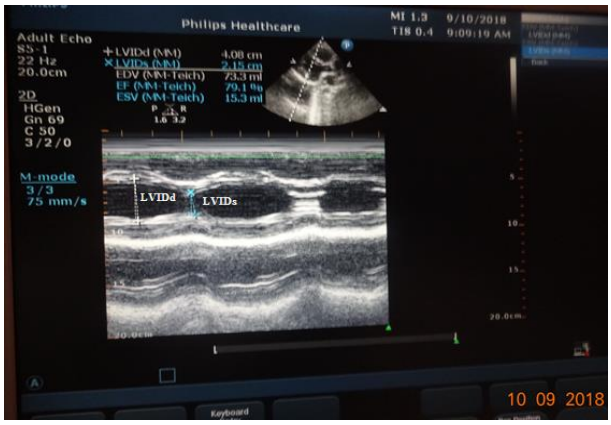

Figure 1: M-mode guided by 2-D echocardiography for LV EF% calculation.

LV mass index (LVMI) and Relative wall thickness (RWT) were then calculated. LV geometry was classified according to the presence or absence of LV hypertrophy defined by an LVM index as accepted by the ASE and the European Association of Cardiovascular classification (13).

Mitral annular plane systolic excursion (MAPSE) was measured in the M-mode while the cursor was placed to the junction of mitral valve (MV) plane with the free wall of the left ventricle (LV) as shown in figure 2 (14).

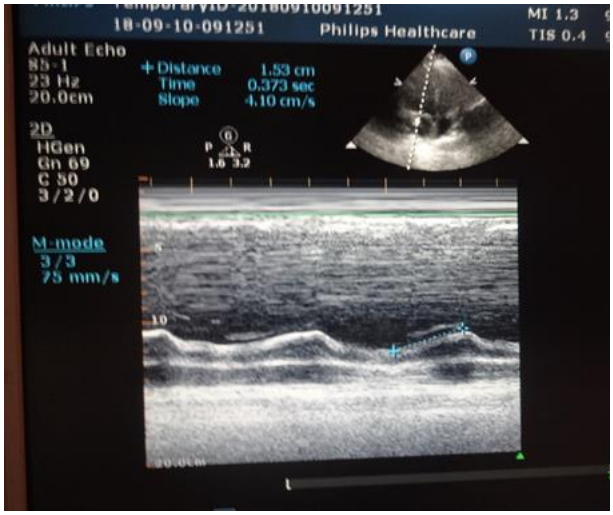

Figure 2: Mitral annular plane systolic excursion measurement.

Transmitral PWD was obtained at the mitral leaflet tips, the peak early (E), late (A) diastolic filling velocities and E/A ratio were recorded (15). TDI with the PWD sample volume placed at the lateral mitral annulus was used to measure the initial first negative (E prime) and a late positive (S prime) wave velocities as shown in figure 3(16).

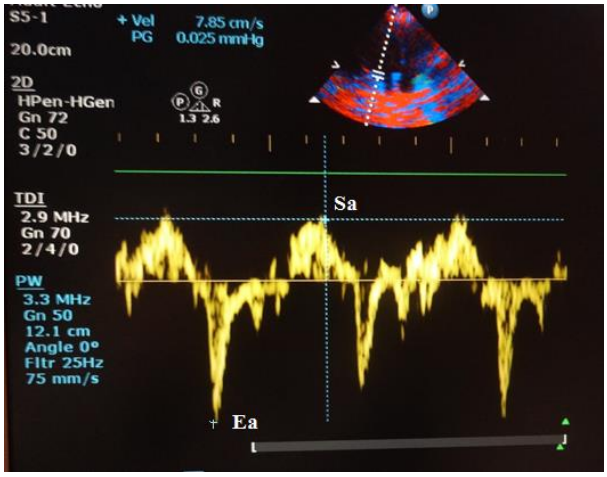

Figure 3: PW tissue Doppler imaging for measuring S prime velocity.

Additionally, LV Speckle-tracking echocardiography was obtained from apical four, three and two-chamber views during stable ECG recording and end-expiratory breath-hold using an offline QLAB-CMQ software program (17). The three-point-and-click method used manually adjustments the region of interest was then done. After that, the software divides the LV myocardium into six parts and generates global longitudinal strain calculated for each view then the global Bull's eye shows an 8-segmental model with averaged global longitudinal strain %. However, the average of three consecutive cardiac cycles was recorded as a strain value as shown in figures 4 and 5(18).

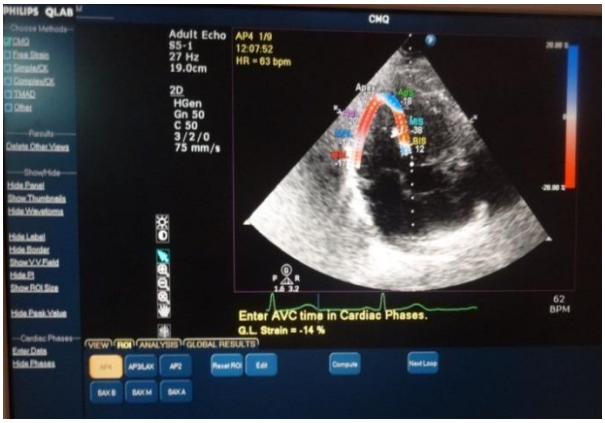

Figure 4: Global LV Strain in 4-chamber view.

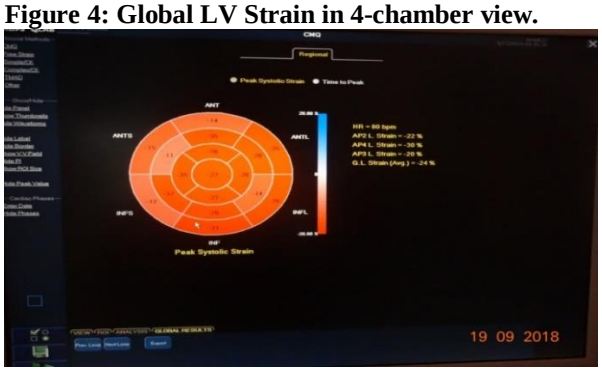

Figure 5: Global longitudinal LV Strain %.

Statistical Analysis:

In this case-control study, data was analyzed using SPSS version 20 for windows. For all tests, a probability value (P-value) of ≤0.05 was considered to be statistically significant. Normally distributed data were presented as mean ± SD for continuous variables. Statistical comparisons among more than two groups were carried out by one-way analysis of variance (ANOVA). Pearson's correlation coefficient (r) was used to test the correlation.

Results:

The studied sample with a mean age of 48± 6.6 years was categorized into three groups according to Doppler studies as:

Group I: Included 76 (73 %) systemic hypertensive patients of either sex; 44 women and 32 men with reversed E/A ratio on PW Doppler and reversed E prime /A prime ratio on PW tissue Doppler with a mean age of 48.41± 6.36 years.

Group II: Included 28 (27%) systemic hypertensive patients of either sex; 17 women and 11 men with normal A ratio on PW Doppler and reversed E

prime/A prime ratio on PW tissue Doppler with a mean age of 49.38 ± 5.32 years.
Group III: Included 104 healthy subjects of either sex; 41 men and 63 women with normal Doppler study served as a control group with a mean age of 48.92 ± 6.03years.

The characteristics and demographic data of the studied groups are shown in Table 1, which demonstrates that they were age, BMI and BSA matched groups (P > 0.05).

Table 1: Anthropometric measurements and blood pressure parameters of the studied groups.

Variables	Group I n = 76	Group II n = 28	Group III n = 104	GIvs. GIII P value	GIIvs. GIII P value	GI vs. GII P value
Age (years)	48 ± 7	48 ± 6	48 ± 7	0.845	0.936	0.759
BMI (Kg/m^2)	26.9± 1.5	26.8± 0.7	26.9±1.3	1.000	0.998	1.000
BSA (m^2)	1.84±0.12	1.79±0.07	1.84±0.1	0.765	0.789	0.985

*BMI= Body Mass Index, BAS= Body surface area.

Table 2 shows that there was a significant difference between the diseased groups regarding the duration of hypertension ((P = 0.005) with a longer disease duration in Group II (9.5 ± 4.23 years) while it was (6.5 ± 4years) in Group I. There was a higher percentage of uncontrolled hypertension in Group II (89.1%) than in Group I (69.7%). A significant difference was found between the studied groups in respect to their systolic blood pressure and pulse pressure being higher in group II with mean systolic blood pressure of (158 ± 15) mmHg and a mean pulse pressure of (69 ± 10) mmHg. However, the diastolic blood pressure results show a significant difference between the diseased and the control groups, with the mean reported in group II (89±9) mmHg.

Table 2: Blood pressure parameters of the studied groups.

Variables	Group I n = 76	Group II n = 28	Group III n = 104	GI vs. GIII P value	GII vs. GIII P value	GI vs. GII P value
Disease duration (years)	6.5 ± 4.23	9.5 ± 4.23	…….	…..	……	0.005
Systolic Bp (mmHg)	151 ±16	158 ± 15	117 ± 5	0.001*	0.001*	0.033*
Diastolic Bp (mmHg)	88 ± 8	89 ± 9	74 ± 7	0.001*	0.001*	0.984
Pulse pressure (mmHg)	61 ± 12	69 ± 10	40 ± 3	0.001*	0.001*	0.001*
Uncontrolled Bp %	69.7	89.1				

*Bp = blood pressure.

Table 3 demonstrates a significant difference (P < 0.05) between all groups regarding IVST, PWT,and RWT being the largest thickness in Group II. While there was a significant difference (P< 0.05) in the LV internal dimensions and volumes (LVIDd, LVIDs,and LVEDV) with the least volume reported in group II (105± 28) ml. The largest mass index was found in the same group (group II). Moreover, LVH was reported in all patients in Group II in addition to a maximum septal thickness was recorded in group II (1.2 ± 0.2cm). LVH was reported only in (71%) of patient in Group I. However, the only type of geometrical changes in LV in both diseased groups was of concentric hypertrophy

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Table 3: Left ventricular geometrical parameters of the studied groups.

Variables	Group I n = 76	Group II n = 28	Group III n = 104	GIvs. GIII P value	GIIvs. GIII P value	GI vs. GII P value
LVIDd (cm)	3.4 ±2.1	3.5 ± 2.1	4.4± 3.4	0.001*	0.001*	0.994
LVIDs (cm)	2.2 ± 1.3	1.9 ±1.3	3.5± 0.6	0.001*	0.001*	0.751
IVST (cm)	1.1 ± 0.3	1.2 ± 0.2	0.77± 0.1	0.001*	0.001*	0.005*
PWT (cm)	1.02 ± 0.3	1.1 ±0.2	0.74± 0.1	0.001*	0.001*	0.001*
LVEDV (ml)	108 ± 26	105± 28	125±7	0.001*	0.001*	0.548
LVESV (ml)	31 ± 15	36 ± 14	38 ± 9	0.627	0.016*	0.587
RWT(cm)	0.48±0.09	0.51±0.06	0.34 ±0.07	0.001*	0.001*	0.006*
LVMI(g/m2)	79 ± 18	88 ± 19	42 ± 6	0.001*	0.001*	0.998
LVH%	71%	100%	0%			

- LVIDd = Left Ventricular Internal Dimensions during diastole, LVIDs= Left Ventricular Internal Dimensions during systole, IVST=inter ventricular septum thickness, PWT = posterior wall thickness, LVEDV=

Left Ventricular End Diastolic Volume and LVESV= Left Ventricular End Systolic Volume, RWT= Relative wall thickness, LVMI = Left Ventricular mass index, LVH=left ventricular hypertrophy.

Table 4 demonstrates the LV function. Regarding the diastolic LV function, the table validates that the peak E velocity was significantly decreased in the diseased groups being the least velocity in group I (72 ± 14) cm/sec while there was a significant decrease in the E prime velocity being the least velocity in group II (6.6 ± 1.19) cm/sec. In addition, there was a significant increase in the E/E prime ratio noticed in the diseased groups being the highest ratio in group II (15.3 ± 0.99). The table shows the LV systolic function to be within normal values in respect to conventional methods with the significant differences being between the diseased groups and the control one regarding left ventricle LV EF% being higher in group II (68± 9%). Furthermore, the S prime measurement shows no significant difference (P> 0.05) between the studied groups with results recorded being more than 11 cm/sec in all groups. Moreover, regarding the last conventional methode which was MAPSE measurement show that there was no significant difference (P > 0.05) between the studied groups with results recorded being more than 12 mm in all studied groups. Howeve, global LV speckle tracking measurement shows a significant difference (P < 0.05) between the diseased groups in comparison to controls with the GLVS% being (-14 ± 1%) in group II and (-16 ± 1) in group I while it was (- 21.9 ± 1) in the control group.

Table 4: Left ventricular function parameters of the studied groups.

Variables	Group I n = 76	Group II n = 28	Group III n = 104	GIvs. GIII P value	GIIvs. GIII P value	GIvs. GII P value
E (cm/s)	72± 14	94± 17	107 ± 7	0.001*	0.001*	0.001*
A (cm/s)	85± 13	79± 25	74± 6	0.001*	0.001*	0 .107
E/A	0.65 ± 2.8	1.75 ± 1.3	1.5 ± 2.1	0.001*	0.001*	0.001*
E prime (cm/s)	6.89± 1.96	6.6±1.19	12.6±1.45	0.001*	0.001*	0.001*
E / E prime	8.06±1.76	15.3±0.99	6.97±0.38	0.001*	0.001*	0.001*
LV EF%	66± 8	68± 9	61 ± 1	0.001*	0.001*	0.895
MAPSE (mm)	15 ± 1	13± 1	17 ± 2	0.029*	0.001*	0 .084
S prime (cm/sec)	9± 1.2	8.7 ± 1.3	10.1± 2.1	0.001*	0.001*	0.999
GLVS %	-16± 1	-14± 1	-22± 1	0.001*	0.001*	0.001*

- LVEF% =Left ventricular Ejection Fraction percentage, MAPSE= Mitral annular plane systolic excursion and GLVS% = Global longitudinal ventricular strain percentage.

Linear regression using Person correlation shows a significant negative linear correlation between GLVS% with that of pulse pressure and IVST respectively (r = -0.25, p = 0.015) (r = -0.22, p = 0.04).

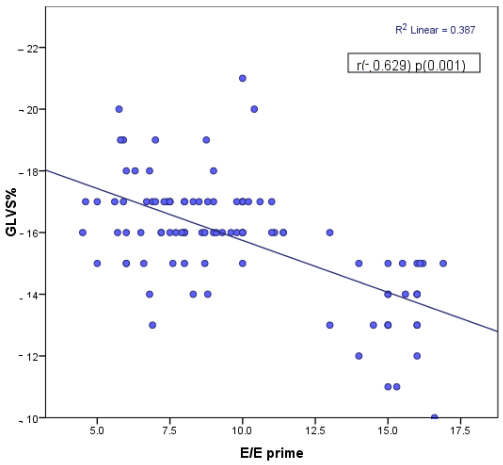

Figure 1: Correlation between GLVS and E/E prime.

The results show a highly significant high negative linear correlation between GLVS% with the of E/A ratio and E/E prime ratio respectively (r = -0.629, p = 0.001) and (r = -0.62, p = 0.001).

Discussion:

The mean systolic and diastolic blood pressure values are in similar to those reported by Muataz et al. and Xu et al (2,19) but are higher than those of Maryam et al. being higher in this study (20). These differences may be related to that most of the patients in the current study are with uncontrolled blood pressure was (69.7% of group I and 89.1% of group II). The RWT is a marker of adverse hypertensive effect on the heart for a long-standing time (21). The estimated RWT of the LV in our study revealed that there was only concentric LVH was seen in all patients in group II and 71% of the patients in group I. This can be explained by the observation that those patients have the highest blood pressure that adversely affects cardiac structure and results in LVH which is a maladaptive response to chronic pressure overload. These results are in concordance with Elmasry et al. and Mizuguchi Y et al. (22, 23) but not in agreement with Izzo et al. (24) which found that all

the patients developed LVH. This may be attributed to the younger age of our study group and the exclusion of those of with risk factors like diabetes mellitus, obesity, and coronary artery diseases. This current study revealed a normal LV systolic function measured by MAPSE and tissue Doppler by measuring S prime velocity. The slightly higher reading of EF% reported in group II (68± 9%) is in agreement with the studies of Sharief K. M. et al., Salam et al. and W.A.I. Hamed et al. (25,26, 27) in which the LVH might be attributed to the explanation of higher EF%.

Diastolic dysfunction can happen in hypertensive patients before systolic dysfunction, which may be due to a noncompliant hypertrophic LV even without obvious signs of heart failure (25, 28). Moreover, delayed LV relaxation with the resultant increased early diastolic pressure, and a reduced transmitral pressure gradient explains the reversed E/A ratio and normal TDI study in group I patients, while in group II patients, the results revealed a higher E velocity and E/E prime ratio due to further deterioration of diastolic function and impedance to atrial emptying. These differences in the LV diastolic function may be related to hypertension that affects LV compliance and decreases in relaxation of the LV. Additionally, the longer duration of hypertension that exacerbates the deterioration in the diastolic function where the duration of hypertension in group II is (9.5 ± 4 y) while in group I is (6.5±4y). This finding is in agrreement with those of Vijaykumar, Ting-Yan Xu et al. and Shantanu et al. (29,19,30). Speckle Tracking Echocardiography is an imaging technique that is used to analyze the tissue motion in the heart by using the naturally occurring myocardial speckle pattern when imaged by ultrasound (31). In respect to global GLVS %, our results demonstrated a reduced global LV longitudinal strain which reflects early changes in systolic function in hypertensive patients being less in group II (-14 ± 1%) than to group I (- 16± 1%). However, the global GLVS% was reduced despite the normal conventional echo parameters (EF%, MAPSE, and S prime measurements). This finding goes in parallel with those of W.Hamed et al. Amal et al. , Kraigher et al. Jun et al. and Minatoguchi S.et al. findings (27, 32, 33, 34, 35). Kraigher et al demonstrates lower GLVS% in heart failure with preserved EF% and in hypertensive patients compared to normal group whereas the others demonstrated impaired systolic function in hypertensive patients using GLVS% with normal EF%. Correlation analysis revealed a significant negative linear correlation between GLVS% with that of pulse pressure and IVST pulse pressure in addition to high negative linear correlations between GLVS% with that of E/A ratio and E/E prime ratio. This can be explained by increased pulse pressure, with the more hypertrophied ventricle with the resultant increased filling pressure of the LV leading to more deterioration in diastolic function with the resultant worsted GLVS%.

Conclusion:

Global left ventricular strain percentage (GLVS%) is a better method in the assessment of LV systolic function in in middle-aged hypertensive patients than conventional echo methods since it can detect an early impairment in LV systolic function despite preserved LV systolic function measured by the conventional echo methods.

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Authors contributions:

Study conception, Critical revision and design: Najeeb Hassan Mohammed and Ghazi Farhan Haji (supervisors).

Acquisition of data analysis, Drafting of manuscript and Interpretation of data: Mahasen Mohammed Abd Al-Majeed, Najeeb Hassan Mohammed and Ghazi Farhan Haji.

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دور تقنية التتبع النقطي ثنائي الابعاد مقارنة بصدى القلب التقليدي في تقييم الوظيفة الانقباضية للبطين االايسر لدى مرضى ارتفاع ضغط الدم الشرياني

د. محاسن محمد عبد المجيد الدوري
أ.د. نجيب حسن محمد
أ.د. غازي فرحان حاجي

الخلاصة:
خلفية البحث:ارتفاع ضغط الدم الشرياني يشكل احد عوامل الخطورة لجهاز القلب والدوران.العلاج المبكرللمرض له دور مهم في تقليل المضاعفات التي تؤثر على عمل وحجم البطين الايسر.
الاهداف:تقييم الوظيفة الانقباضية للبطين االايسربتقنية التتبع النقطي ثناي الابعاد مقارنة بصدى القلب التقليدي
المرضى وطرق العمل:تمت دراسة 104 مريض مصاب بارتفاع ضغط الدم، مجموعة 1 وشملت 76 مريض مصاب بقصور عمل البطين الايسر الانبساطي من الدرجة الاولىبينما المجموعة 2 شملت 28مريض مصاب بقصور عمل البطين الايسر الانبساطي من الدرجة الثانية اضافة الى مجموعة 3شملت 104 شخص من الاصحاء كمجموعة ضابطة علما ان اعمار المجاميع الثلاث تتراوح بين 35-55سنة ومن كلا الجنسين وتم اخضاعهم للفحص السريري وقياس ضغط الدم وفحوصات صدى القلب للبطين الايسر الانبساطية والانقباضية
النتائج:اظهرت النتائج ان تقييم عمل البطين الايسربتقنية نسبة الكسر القذفي (EF%) بتقنية تصوير دوبلر النسيجية (TDI-S prime)والانحراف الانقباضي لحافة الصمام التاجي(MAPSE) كانت طبيعية بينما كانت نتيجة تقنية التتابع النقطي باستخدام نسبة الاجهاد الطولي للبطين الايسر(GLVS%) تثبت قصورا ملحوظا المجموعة 1 (-13.54± 1.5%) مجموعة2(-16.55± 1.4%)وكان القصور مرتبط ارتباطا وثيقا بالضغط النبضي وسمك حاجز القلب البطيني وموشرات البطين الايسر الانبساطية
الاستنتاجات: امكانية الكشف المبكر عن القصور في عمل البطين الايسر الانقباضي عن طريق تقنية التتابع النقطي باستخدام معامل نسبة الاجهاد الطولي للبطين الايسر لدى المرضى المصابين بارتفاع ضغط الدم الشرياني بالرغم من نتائج الفحص الطبيعية باستخدام التقنيات التقليدية
مفتاح الكلمات:ارتفاع ضغط الدم الشرياني،تقنية التتابع النقطي، تقنية تصوير دوبلر النسيجية

Open Access Original Article

Ultrasound Findings of Mammographically Dense Breasts in a Sample of Iraqi Female Patients

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Khaleel I. Mohson* **DMRD, CABMS**
Tara F. Kareem** **CABMS**
Anas K. Awn* **MBChB**

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Abstract:

Background: Breast problems including breast cancer have been increasing in Iraq during the recent years. Yet, early detection and screening programs using mammography mainly with complementary ultrasound had dramatically decreased the mortality rates from this emerging disease.

Objective: To assess the dense breast detected by mammography for the presence of any hidden suspicious lesion by using ultrasound.

Patients and methods: this is a cross-sectional study on 53 female patients who came for breast cancer screening or attended the Breast Clinic in the Oncology Teaching Hospital of the Medical City Complex in Baghdad – Iraq. The study was conducted from January to October 2018. Two-view mammography was done for each breast, and those with dense breasts underwent further ultrasound assessment done by a board-certified radiologist.

Results: The mean age for the 53 patients included in the study was 48 years. Mammographic findings showed that heterogeneous fibroglandular tissue density was present in (89%) of the study population. Suspicious or clearly defined mass(es) by mammograph were seen in 16 (30%) of the patients, while no mass was identified in (22%). Ultrasound findings were as follows: Suspicious mass in (75%) of the cases and benign lesions such as simple cysts or fibroadenoma in (9%). The results showed that ultrasound has upgraded 12 cases that were diagnosed as BI-RADS I/II to BI-RADS IV/V and this represented (23%) of the cases. On the other hand, the mammogram and the ultrasound were in concordance for BI-RADS IV/V in 28 cases (54%). The positive predictive value of the ultrasound and the mammogram for BI-RADS IV and V breast lesions is 72% for BI-RADS IV and 95% for BI-RADS V for ultrasound and that of mammograph is 83% for BI-RADS IV 80% for BI-RADS V, while the negative predictive value of mammograph is 55% for BI-RADS I/II 25% for BI-RADS III.

Conclusion: Dense breast is still an important problematic issue in mammographic screening as it may obscure small lesions, for which, ultrasound is proved to be a complementary and essential targeting tool in the assessment process.

Keywords: Dense breasts, mammography, breast cancer screening, breast ultrasound.

Introduction:

Breast cancer is the leading cause of death in Iraqi women according to Iraqi cancer registry [1]. The best way to reduce that is by screening and early detection that was achieved by using mammography which is considered to be the first line modality for breast cancer screening that was shown to reduce the mortality by 40% when used in women under the age of forty [2].

However, in spite of powerful cancer detection by mammography, it is still weak in patients with dense breasts, in whom cancer detection sensitivity was decreased from 85% to about 46-65% [3]. Breast density is defined as the consistency of breast according to the relative amounts of fat and glandular tissue and hence four categories were established according to the American College of Radiology's breast imaging reporting and data system (BI-RADS) which includes four categories: (A) almost entirely fatty, (B) scattered fibro-glandular tissue, (C) heterogeneous glandular breast and (D) an extremely dense breast[4]. According to these categories, detecting the pathology by mammography was imperfect in both categories C and D as those were considered as dense breasts while each category A and B are regarded as non-dense breasts [4]. Dense breast tissue is common and represents more than 50% of women younger than 50 years while this percentage decreases to 30% of women aged over 50 years [5]. To solve the dense breasts problem as a false negative cause on mammography, alternative solutions and strategies were employed including frequent screening sessions [6]. The previous solution is somewhat costly, with more radiation effects and

* *Iraqi National Cancer research center Corresponding Email: khalelcabms@gmail.com Anas.awn85@gmail.com*
**Oncology Hospital/ Medical City tarafaroukkareem@gmail.com*

more importantly the mammography is less accurate in the dense breast and therefore it was preferable to use a different radiological modality better than repeating the mammography several times [7].

For these reasons, the desire to use ultrasound as an adjuvant to mammography in the assessment of the dense breast tissue has emerged [8]. Ultrasound is simple, likable examination modality, as it is available, well accepted by patients, usually performed using high-resolution linear transducers that permit detailed depiction of solid and even small masses, also for it lacks ionizing radiation [9].

Women with dense breasts are five-folds more susceptible to develop breast cancer than those with soft ones. Not only that, but the tumor is often larger and usually spreads more to the loco-regional lymphatics [10, 11]. Furthermore, the Interval breast cancer also comes with higher rates [12].

Patients and Methods:

The study was conducted on 53 female patients who attended the Breast Clinic in the Oncology Teaching Hospital of the Medical City Complex in Baghdad – Iraq, from January to October 2018. They presented complaining of pain or a mass, or those who came to check. The clinical examination was done by a specialist general surgeon, which when revealed non-significant abnormality, they were referred to the radiology department for mammography. Mammography was performed by a specialist operator using GE healthcare seno essential digital mammography. During mammography, the patient had her breasts fully exposed and compression paddles were used with two projections, mediolateral oblique and craniocaudal, the mammography film was read by a specialist radiologist and revealed either heterogeneous or extremely dense breasts with no suspicious mass. The patients, then underwent breast ultrasound using Siemens Voluson E6 machine where they were asked to lie down supine on the examination couch with both breasts and axillae completely exposed and each breast was examined in a radial pattern using a GE machine's linear probe 5-12MHz. Following the breast examination, the axilla was fully assessed for any pathological adenopathy. All variables and findings were recorded including the following: Mammography: Breast density, presence or absence of a mass, micro calcification, macro calcification, skin thickness and axillary adenopathy

Ultrasonography: Breast echotexture, ductal dilatation, mass lesion (solid or cystic), skin thickening and axillary adenopathy.Any suspicious lesion seen by ultrasound was subjected to Fine needle aspiration donw by cytologist under ultrasound guide.

Statistical analysis

All women's data were entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics were presented as (mean ± standard deviation) and frequencies / percentages.

Results :

The age range for the patients in the study was 36 - 60 years with a mean age of 48 years. Over half of the patients were in the 6th decade. The age distribution is further detailed in table (1).

Table (1): Age distribution of the cases

Age (Years)	Number	Percentage
30-39	4	7.5 %
40-49	22	41.5 %
50-60	27	51%
Total	53	100%

Regarding the mammographic findings in the study group, the extremely dense glandular breasts were seen in 7 out of 53 (11%) of the patients, while the mammograph in the remaining patients (89%) showed heterogeneous fibroglandular tissue density. Suspicious or clearly defined mass(es) by mammograph were seen in 17 (32%) of the patients, no mass were identified in (22%) of the sample. Other findings detected by mammograph were skin thickening, glandular asymmetry, positive axillary lymph nodes, and micro calcification, table (2) illustrates more details about the above mentioned findings.

Table (2): Mammographic findings

Mammographic findings	Number	Percentage
Mass	17	32.0%
No mass	12	22.6%
Skin thickening	9	17.0%
Extremely dense glandular breast	7	13.2%
Positive axillary lymph nodes	3	5.7%
Glandular asymmetry	3	5.7%
Microcalcification	2	3.8%
Total	53	100.0%

The majority of BI-RADS scores identified by mammography: BI-RADS IV was seen in 20 (37.7%) of the patients, BI-RADS I and II were seen in 19 (36%) of the patients, patients with BI-RADS III were 7 (13%) and finally, BI-RADS V was seen in 7 (13%) of the patients. the ultrasound findings were as follows: Suspicious mass in (75%) of the cases, and benign lesions such as simple cysts or fibroadenoma in (9%). Other findings included skin thickening, benign adenopathy, thick cortex lymph nodes and distorted hilum adenopathy, as shown in the table (3).

Table (3): The ultrasonographic findings

Ultrasonographic Findings		Number	Percentage
Suspicious (speculated or ill-defined mass)		40	75%
Benign mass		5	9%
Skin thickening		9	17%
Lymph Adenopathy	Benign	10	19%
	Thick cortex	5	9%
	Distorted hilum	7	13%

In patients with heterogeneous or extremely dense breast, a test was performed to measure if there is a significant BI-RADS difference between the ultrasound and the mammogram in the field of cancer detection, the results showed that ultrasound has upgraded 12 cases that were diagnosed as BI-RADS I/II to BI-RADS IV/V and this represented (23%) of the cases. Otherwise, the mammogram and the ultrasound were in concordance for BI-RADS IV/V in 28 cases (54%). The Accuracy of the ultrasound and the mammogram for BI-RADS IV and V breast lesions in comparison with cytopathology through the use of fine needle aspiration cytology, the negative predictive value for mammography regarding the BI-RADS I/II and III by considering the ultrasound and fine needle aspiration cytology as references for true negative and false negative, the results are 55% for BI-RADS I/II and 25% for BI-RADS III, the detailed results are shown in the table (4).

Table (4): The accuracy of the ultrasound and mammography for BI-RADS IV and V lesions in comparison with cytopathology

Ultrasound BI-RADS Score	Fine Needle Aspiration Cytology	
	Benign	Malignant
IV	8	16
V	1	19
Positive Predictive Value	72% for BI-RADS IV 95% for BI-RADS V	
Mammography BI-RADS Score	Fine Needle Aspiration Cytology	
	Benign	Malignant
IV	3	15
V	2	8
Positive predictive value	83% for BI-RADS IV 80% for BI-RADS V	
Mammography BI-RADS Score	Fine Needle Aspiration Cytology	
	Benign	Malignant
I, II	11	9
III	1	3
Negative Predictive Value	55% for BI-RADS I/II 25% for BI-RADS III	

Discussion:

The breast cancer mortality has been significantly reduced since the introduction and the progression in screening programs using mammography [13]. Strict standards have been developed to improve and maintain the quality of this program [14]. Mammography sensitivity is decreased with dense breasts [15]. Therefore, performing breast ultrasoonography is of great benefits that outweigh the BI-RADS overestimation or underestimation. [16] The mean age in the current study population is within the late 5th decade. BI-RADS I, II and III scores detected by mammography represented 45% of the cases, while BI-RADS IV represented 36%. This is in agreement with a study carried out by Hooley in 2018[17]. Ultrasound BI-RADS score revealed that 17% of the patients were in scores I, II but it came significantly higher for BI-RADS IV and V where they represented 82% which is in agreement with a study done by Berg et al [18]. Regarding the ultrasound positive predictive values for BI-RADS IV and V lesions, they were 72% and 95% respectively which was comparable to the mammography predictive results for the same BI-RADS scores which represented 83% and 80% respectively. Accordingly, mammography predictive values are still lower than those of the ultrasound for BI-RADS V lesions, mainly because of the high breast density obscuring cancers, especially the small ones that get easily overlooked with dense breast tissues. These findings are relatively in agreement with a study done by Moshina et al [19]. Mammography negative predictive values for BI-RADS I, II and III collectively represented 80%, which was closely in concordance with the study conducted by Masroor et al on a nearly similar study group, with patients complaining of mastalgia. Differences between the two studies may be attributed to the selection of patients with dense breast tissues, and to racial differences [20]. Mammography results were found to be false negative in 26% of the cases while ultrasound was true positive in 73% of them. This indicates that the complementary use of the ultrasound is mandatory in the setting of heterogeneous and extremely dense breasts, which was in agreement with the study done by Devolli-Disha et al [21].

Conclusion:

Dense breasts represent a diagnostic challenge to the radiologist, especially in high-risk populations where the breast cancer comes to be as the leading cause of death among other cancers, so adding breast ultrasound in this setting is mandatory especially when performed by highly qualified radiologists.

Author's Contributions:

Dr. Khaleel Ibraheem Mohson, Dr. Tara Farook: collect the data, made the design of the study, Dr. Khaleel and D. Anas K.Awn were writing the manuscripts in addition.

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مشاهدات الفحص بالموجات فوق الصوتية (السونار) للثدي ذو الكثافة العالية في جهارالماموجرام لعينة من النساء العراقيات

د. خليل محسن ابراهيم
د. تارة فاروق كريم
د. انس خيري عون

الخلاصة:
الخلفية: مشاكل الثدي بما في ذلك سرطان الثدي في تزايد في العراق خلال السنوات الأخيرة، ومع ذلك، فإن برامج الكشف المبكر والفحص باستخدام التصوير الشعاعي للثدي (بشكل رئيسي) ومساعدة الموجات فوق الصوتية كفحص تكميلي قد خفضت معدلات الوفيات بشكل كبير من هذا المرض الخبيث.
المرضى وطرق البحث: شملت الدراسة 53 مريضة أتين للكشف عن سرطان الثدي في مستشفى الأورام التعليمي التابع لمجمع مدينة الطب في بغداد - العراق. خلال الفترة من يناير حتى أكتوبر 2018. تم إجراء تصوير الثدي بالأشعة لكل ثدي ثم خضعت المصابات بثدي ذو كثافة نسيجية عالية إلى مزيد من التقييم بالموجات فوق الصوتية من قبل أخصائي الأشعة.
النتائج: من بين 53 مريضة في الدراسة كان متوسط العمر 48 سنة، فيما يتعلق بنتائج الماموكرافي في عينة الدراسة، وجدت كثافة الأنسجة الليفية غير المتجانسة في (89٪) من عينة الدراسة. وشوهدت كتلة مشبوهة بوضوح بواسطة التصوير الشعاعي للثدي في 16 (30٪) من المريضات، ولم يتم تحديد أية كتلة في (22٪) من العينة، وشملت نتائج الموجات فوق الصوتية على النحو التالي: كتلة مشبوهة في (75٪) من الحالات، والآفات الحميدة كأكياس بسيطة أو ورم غدي ليفي في (9٪)، أظهرت النتائج أن الموجات فوق الصوتية قد رفعت 12 حالة تم تشخيصها بأنها بايراد 1 و2 الى بايراد 4 و5 وهذا يمثل (23٪) من الحالات.
الإستنتاج: لا يزال الثدي ذو الكثافة النسيجية العالية مشكلة هامة في الفحص باشعة الماموكرام، حيث أنه قد يحجب الآفات الصغيرة، لذلك ثبت أن الموجات فوق الصوتية هي أداة تشخيص تكميلية وأساسية في عملية التقييم في الحالات اعلاه.
مفتاح الكلمات: الثدي الكثيف، التصوير الشعاعي للثدي، فحص سرطان الثدي، تصوير الثدي بالموجات فوق الصوتية.

Open Access Original Article

Risk factors of hearing defects and their relationship to the outcome of hearing screening among neonates

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Numan N. Hameed* (MD, FRCPCH, FIBMS, MRCPCH)
Mokhalad G. Malih (MD, MBChB)**

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Abstract:

Background: Increased exposure to risk factors of hearing loss leads to a high susceptibility to deafness among neonates admitted to neonatal care units in developing countries.

Objective: This article aims to study the prevalence of risk factors for neonatal hearing defect and determine their effect on the result of transient evoked otoacoustic emissions hearing test (TEOAE).

Methods: A longitudinal study was carried out for a period of one year from 1st October, 2016 to 30th September, 2017 in the CWTH, Medical city, Baghdad, Iraq. Demographic characteristics and certain risk factors were recorded for screened neonates. TEOAE test was done and if they failed to pass two steps, they were referred to automated auditory brainstem-response (AABR).

Results: Out of 400 neonates, 342 (85.5%) passed from step 1 TEOAE, while 58 (14.5%) were referred to step 2. From 58, 26 (44.8%) have passed step 2 and 32 (55.2%) not pass step 2 and were referred to AABR. From those 32 neonates with suspected hearing defect, NICU stay >7 days, ototoxic drugs >7 days, use of ventilator >7 days, birth weight <1500gm, and craniofacial malformations were the main risk factors for hearing defects occurring in (90.6%), (90.6%), (59.4%), (40.6%), and (21.9%) respectively.

Conclusions: Low birth weight, long intensive care stay, mechanical ventilation, drugs ototoxicity and craniofacial malformation of neonates are the main risk factors for failed TEOAE test.

Keywords: Hearing defect, Hearing Screening, Neonates, Risk Factors.

Introduction:

Hearing loss (HL) is one of the common congenital problems among neonates [1]. The prevalence of significant HL ranges from 1.2 per 1,000 healthy newborn infants and 2 to 5% in high-risk newborns [2, 3]. Nearly 50% of congenital HL is due to genetic defects [1]. About 50% of hearing defects can be detected in a selective screening based exclusively on hearing risk criteria [1]. Early detection and intervention at a younger age are critical for future speech, language and cognitive development. Neonates with congenital HL should be identified within the first 3 months of life. However, the average age at detection is currently 24-30 months [4]. Hearing assessment can be done either by Transient evoked Otoacoustic emission (TEOAE) or by Automated Auditory Brainstem Response (AABR). OAEs provide a simple, efficient and non-invasive objective indicator of healthy cochlear function. OAEs may be either spontaneous or induced by acoustic stimulation. TEOAE is an effective method for neonatal audiological screening both in the general population and in high-risk infants [5].

* *Department of Pediatrics, College of medicine, Baghdad University.*
Correspondence
Email:numanalhamdani@Yahoo.com
** *Children welfare teaching hospital, medical city.*
Email: m_g_plus@yahoo.co.uk

Risk factors associated with HL were identified by the Joint Committee on Infant Hearing (JCIH) in 2007 [6]. The use of risk factors is no longer recommended to select children who should undergo hearing screening. Studies have shown that only 50% of the pediatric population with congenital HL would be identified by this procedure. However, it is essential to identify risk factors for HL, because an infant with any of these factors in neonatal history has a greater chance of experiencing HL. Additionally, it can guide the approach to be adopted after the results of the hearing screening [7]. Newborn hearing screening was initially targeted toward those newborn ‘‘at risk’’ for HL called High-Risk Register (HRR) [6].This group included infants who had asphyxia, meningitis, congenital or perinatal infections, anatomic defects or stigmata, hyper-bilirubinemia, family history of HL, low birth weight, ototoxic medications, and neonatal illnesses requiring mechanical ventilation. HRR screening resulted in around 50% of congenital HL being undetected [8]. It was soon realized that a more logical approach is to implement universal newborn hearing screening aiming at the early identification of most, if not all children with congenital HL[9]. This study Aimed to find out the prevalence of risk factors for neonatal HL and determine their relationship the result of TEOAE hearing test in neonates referred and admitted to NICU of Children Welfare Teaching Hospital, Medical City, Baghdad.

Patients and Methods:

A longitudinal study was carried out for the period from 1st October, 2016 to 30th September, 2017 in the CWTH, Medical city, Baghdad, Iraq. This 250 beds tertiary hospital had 34 incubators and a level 3Neonatal Intensive Care Unit (NICU) which receives infants referred from other hospitals, primary health centers and private clinics for further management of neonates. Inclusion criteria include all neonates less than 28 days old who were referred to hospital for screening from other NICUs and discharged well. Exclusion criteria included neonates who failed in the step 1 of screening and have not attended the second one, and those whose parents refused participation due to deteriorated health status. Data was collected from the parents and the neonates` discharge cards in the outpatient neonatology clinic and case sheets of neonates admitted to NICU/CWTH through direct interview and filling the prepared data collection sheet. The data collection sheet was designed by the researchers depending on the experience of previous international literatures. The questionnaire included the followings: Demographic characteristics, age and gender of neonates, gestational age of neonates, gestational history, type of delivery, birth weight, consanguinity and craniofacial malformations, family history of HL, clinical history, NICU stay duration, sepsis, meningitis, use of ventilator, ototoxic drugs, hyperbilirubinemia and exchange transfusion, Results of step 1-TEOAE, and results of step 2-TEOAE. After identifying eligible neonates, their data was collected and a TEOAE hearing test was performed by a well-trained healthcare provider. Neonates who have passed the 1st step were considered normal. The 2nd TEOAE test was performed after two weeks for a neonate who had failed the 1st test. They were referred to AABR to complete the assessment of their hearing if they failed the 2nd TEOAE hearing test. TEOAE test was carried out for both ears using the ILO Echo-check system, a portable device which uses click stimuli involving frequency bands between 1,500 Hz and 3,800 Hz. The click is presented at an intensity of 75 to 83 dBpeSPS. The response was considered positive (pass) when the otoacoustic emissions captured were 6 dB higher than the noise. Approval to conducts the study was obtained from the Ethical committee of CWTH. Oral informed consent was taken from neonates` parents by the health care provider. The neonates were screened as part of the hospital policy to screen all neonates who came to CWTH neonatology outpatient clinic and admitted neonates to NICU before discharge. The data of screening were collected from registry of hearing screen room.

Statistical analysis:

All patients' data were analyzed using Statistical Package for Social Sciences (SPSS) version 22. Descriptive statistics were presented as (mean ± standard deviation) and frequencies / percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Chi square test was used test the association between categorical data (Fishers exact probability test was used when expected variables were less than 20% of total). Independent sample t-test was used to compare between two means. The level of significance (p value) was set at ≤ 0.05.

Results:

A total of 400 neonates screened for HL were included with mean age of 19±8 days. Two-hundred and thirty (57.5%) screened neonates were males and 170 (42.5%) were females with male to female ratio of 1.3:1. The mean gestational age (GA) was 35.3±3.3 weeks; 4 neonates (1%) were born before 28 weeks of gestation, 34 (8.5%) were 28- <32 weeks of GA, 208 (52%) were 32- <37 weeks of GA and 154 (38.5%) were ≥37 weeks of G.A. of 400 screened neonates, 161 (40.2%) were delivered vaginally (VD), while 239 (59.8%) were delivered by cesarean section (CS). Birth weight less than 1500g was found in 95 neonates (23.7%). Consanguinity was found in 204 (51%). Craniofacial malformations were found in 30 neonates (7.5%). A positive family history of HL was found in 22 neonates (5.5%). The mean NICU stay duration was 11±6 days, 128 (32%) neonates stayed ≤7 days and 272 (68%) had stayed more than 7 days. History of sepsis was present in 171 (42.8%), meningitis in 34 (8.5%), on ventilation >7 days in 70 (17.5%), on ototoxic drugs >7 days in 271 (67.8%), significant hyperbilirubinemia in 216 (54%) and requiring exchange transfusion in40 (10%) of neonates (Table 1).

Table 1: Clinical history of 400 neonates

Variable	No.	%
NICU stay duration mean ±SD (11±6 days)		
≤7 days	128	32.0
>7 days	272	68.0
Sepsis	171	42.8
Meningitis	34	8.5
Ventilator >7 days	70	17.5
Ototoxic drugs >7 days	271	67.8
Significant hyperbilirubinemia	216	54.0
Exchange transfusion required	40	10.0
Total	400	100.0

Of 400 screened neonates, 342 (85.5%) passed step 1 TEOAE while 58(14.5%) were referred to step 2 TEOAE. Of those 58 neonates referred to step 2 TEOAE, 26 (44.8%) have passed step 2 while 32 (55.2%) have failed it and were referred to AABR. Neonates referred to AABR represented 32 (8%) of total screened neonates. There was no significant association between gender and being referred to AABR. A significant association was found between referral to AABR and lower GA (p=0.02) (Table 2).

Table 2: Distribution of neonates' gender and gestational age according to TEOAE passing (No AABR) and referral to AABR

Variable	AABR		No AABR		Total	χ^2	P
	No.	%	No.	%			
Gender						0.2	0.6
Male	17	7.4	213	92.6	230		
Female	15	8.8	155	91.2	170		
Gestational age						9.8*	0.02 *Signi-ficant*
≥37	10	6.5	144	93.5	154		
32 - <37	14	6.7	194	93.3	208		
28 - <32	7	20.6	27	79.4	34		
<28	1	25.0	3	75.0	4		

Fishers exact probability test

No significant associations were detected between neonates being referred to AABR and the type of delivery, consanguinity and family history of HL. A significant association between low birth weight and referral to AABR (p=0.01) was detected as well as a highly significant association between craniofacial malformation and referral to AABR (p<0.001), (Table 3).

Table 3: Distribution of obstetrical and family history according to TEOAE passing (No AABR) and referral to AABR

Variable	AABR		No AABR		Total	χ^2	P
	No	%	No.	%			
Type of delivery						0.6	0.4
Vaginal	15	9.3	14	90.7	161		
CS	17	7.1	22	92.9	239		
Birth weight <1500gm						5.4	0.01 *Sig*
Yes	13	13.	82	86.3	95		
No	19	6.2	28	93.8	305		
Consanguinity						0.3	0.5
Positive	18	8.8	18	91.2	204		
Negativ	14	7.1	18	92.9	196		
Craniofacial malformation						10.3 *	0.00 1 *High*
Yes	7	23.	23	76.7	30		
No	25	6.8	34	93.2	370		
Family history of hearing loss						2.1*	0.1
Positive	0	0	22	100.	22		
Negativ	32	8.5	34	91.5	378		

Fishers exact propability test

There was no significant association between neonates being referred to AABR and having sepsis, meningitis, hyperbilirubinemia and exchange transfusion. There was a significant association between referral to AABR and increased NICU stay duration (p=0.004), neonates on ventilator for >7 days (p<0.001) and ototoxic drugs use for >7 days (p=0.004), (Table 4).

Table 4: Distribution of neonates' clinical history according to TEOAE passing (No AABR) and referral to AABR

Variable	AABR		No AABR		Total	χ^2	P
	No.	%	No.	%			
NICU stay duration						8.1	0.004 *Sig*
≤7 days	3	2.3	125	97.7	128		
>7 days	29	10.7	243	89.3	272		
Sepsis						2.5	0.1
Yes	18	10.5	153	89.5	171		
No	14	6.1	215	93.9	229		
Meningitis						0.03	0.8
Yes	3	8.8	31	91.2	34		
No	29	7.9	337	92.1	366		
Ventilator >7 days						42.2	<0.001 *High*
Yes	19	27.1	51	72.9	70		
No	13	3.9	317	96.1	330		
Ototoxic drugs >7 days						8.3	0.004 *Sig*
Yes	29	10.7	242	89.3	271		
No	3	2.4	126	97.6	129		
Hyperbilirubinemia requiring phototherapy or exchange transfusion						0.4	0.5
Yes	19	8.8	197	91.2	216		
No	13	7.1	171	92.9	184		
Exchange transfusion required						0.01	0.9
Yes	3	7.5	37	92.5	40		
No	29	8.1	331	91.9	360		

Discussion:

Completeness of children auditory system is an essential requirement and one of the prerequisites for earning a complete oral language and intellectual development by communicating with their families, understanding the world, interaction with other children, thoughts and feeling development and acquisition of knowledge [10]. In the current study 32 (8%) of the neonates were referred to AABR after screening with two steps of TEOAE. This prevalence of suspected HL is close to results of Oliveira et al in Brazil who reported that among 1146 screened neonates, 82 (7.2%) failed TEOAE and were referred to AABR [11]. The prevalence is higher than that found by Gouri et al in India (5.3%) [12], but lower than that found by Pourarian et al in Iran (13.7%) [13] and Olusanya et al in Nigeria (4.1%) [14]. High prevalence of suspected neonates with HL might be attributed to the fact that CWTH is a tertiary center mainly receiving complicated cases from other governorates. The current study revealed 58 (14.5%) neonates were referred to step-2 TEOAE, from whom 32 (55.2%) were referred to AABR. These findings are higher than the results of Habib et al in Saudi Arabia[15],who found that among 11986 neonates screened with step 1-TEOAE, 1043 (8.7%) neonates were referred to step-2 TEOAE, from whom 300 (27%) failed and were referred to AABR. The higher rate of referrals to step-2 TEOAE test (false positive step-1) could be due to local causes like wax accumulation or otitis media (with or without effusion) or due to an improper external environment like noise. Kumar et al[16] stated that TEOAE had a high accuracy in early detection of congenital HL, in spite of the high false negative rate found by many studies.[17,18] TEOAE has limited activity in the categorization of risk factors for HL among high risk population[19] in addition to many disadvantages of screening use among neonates [16,20]. Despite these findings, TEOAE represents the major non-invasive instrument for early detection of HL of cochlear origin, as it focuses on mechanical function in addition to TEOAE cost-effectiveness that facilitates its application in developing countries.[21] Low GA of neonates was significantly associated with failed step-2 TEOAE hearing test (p=0.02). This finding coincides with the results of Waters et al [22] in the USA. Infants born with lower GA were exposed to delayed myelination of the central nervous system and hearing bones development [23]. Some studies suggested that the main causes of hearing impairment among low GA infants are cochlear immaturity in

pre-term neonates and middle ear effusion due to prolonged tracheal intubation [16, 18]. Similarly, the current study showed a significant association between low birth weight (<1500 gm) and failed step-2 TEOAE (p=0.01). This finding is consistent with results of Onoda et al in Brazil [24]. Many authors found a strong relationship between birth weight and failed hearing screening tests in addition to HL[25].The very low birth weight has multiple risk factors for hearing problems like birth asphyxia which needs long NICU admission, mechanical ventilation and ototoxic medications[26]. Gender of the neonate was not significantly associated with failing TEOAE. This finding is similar to results of Karaca et al in Turkey[27].Consanguinity and family history of HL were not found to be related to neonatal hearing problems, in contrast to the results of Shrikrishna et al in India who reported that consanguinity and family history are common risk factors of genetic neonatal HL[28]. Neonates with craniofacial malformations had significantly higher rates of failed TEOAE (p=0.001), similar to report of Lunardi et al in Italy [29]. Craniofacial malformation is related mainly to developmental abnormalities of the first and second branchial arches, which contribute to development of the hearing system (skeletal, muscular and nervous) [29]. NICU stay duration was significantly related to failed TEOAE hearing tests (p=0.004), in consistence with the results of Barboza et al in Brazil [30]. Long NICU stay duration is usually relevant to deteriorated health of infants, prematurity, mechanical ventilation and ototoxic antibiotic use [31]. Use of ventilators for more than 7 days was significantly related to failed TEOAE screening test (p<0.001), in consistence with results of Amini et al in Iran [32]. Continuous nasal positive airway pressure applied as a respiratory support for preterm neonates proved to be a risk factor for prolonged exposure to high levels of noise [33]. The current study revealed that ototoxic drugs used for neonates were significantly associated with failed TEOAE screening (p=0.004), which is in agreement with the results of So et al in the USA [34], who documented that the use of bolus doses of ototoxic drugs especially aminoglycosides is highly related with neonatal HL and that over therapeutic serum levels of aminoglycosides have shown an increased possibility of ototoxicity. Since aminoglycoside serum concentrations were not measured in our study, there is a high probability that those neonates who had failed TEOAE screening might have had high serum levels while receiving aminoglycosides and eventually had an increased risk of ototoxicity, especially when these drugs were given for long periods. The concern of many literatures was the delayed effect of aminoglycosides in development of sensory neural HL [35]. Although no significant relationship was demonstrated between failing TEOAE and each of sepsis, meningitis, hyperbilirubinemia and exchange transfusion, many studies had reported neonatal sepsis and high bilirubin level of neonates as independent risk factors for HL among neonates [36, 37]. This inconsistency with our findings might be due to differences in health services in addition to differences in study design.

Conclusions:

Prematurity, low birth weights, craniofacial malformation, long NICU stay duration, mechanical ventilation and drugs ototoxicity were found to be risk factors for failed transient evoked otoacoustic emissions hearing test in screened neonates in Children Welfare Teaching Hospital. The study recommends encouraging routine hearing screening programs for neonates especially those at risk like preterm, low birth weight, malformation and admission to NICUs. Larger national longitudinal multi-center studies applying other screening and diagnostic hearing tests must be supported.

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عوامل اختطار عيوب السمع وعلاقتها بنتيجة فحص السمع بين الولدان

الاستاذ الدكتور نعمان نافع حميد الحمداني- فرع طب الاطفال- كلية الطب – جامعة بغداد ومستشفى حماية الاطفال – مدينه الطب
الدكتور مخلد غازي مالح- طبيب مقيم اقدم - مستشفى حماية الاطفال – مدينه الطب

الخلاصة:
خلفية: يؤدي التعرض المتزايد لعوامل الخطر لفقدان السمع إلى زيادة التعرض للصمم بين الولدان المولودين في البلدان النامية.
اهداف الدراسة: تهدف هذه المقالة إلى دراسة مدى انتشار عوامل الاختطار لعيوب السمع عند الأطفال حديثي الولادة وتحديد تأثيرها على نتيجة اختبار السمع الصوتي الناتج عن الانبعاثات.
الطريقة: أجريت هذه الدراسة الطوليه لمدة سنة واحدة. تم تسجيل الخصائص الديموغرافية وبعض عوامل الاختطار. وإذا لم يتمكنوا من اجتياز خطوتين، فقد تمت إحالتهم إلى الاستجابة الدماغية السمعيةللولدانتم إجراء اختبار(AABR).
النتائج: من أصل 400 حديث الولادة، اجتاز 342 (85.5٪) الخطوة الأولى من اختبار السمع الصوتي الناتج عن الانبعاثات، في حين تمت إحالة 58 (14.5٪) إلى الخطوة الثانية. ولقد اجتاز 26 (44.8٪) الخطوة الثانية بينما لم يجتز الخطوه الثانيه 32 (55.2٪) وقد احيلوا الى فحص الاستجابة الدماغية السمعية.وكانت اهم عوامل الاختطار الرئيسية لعيوب السمع في 32 مريض هي مدة البقاء في وحدة العنايه المركزة لاكثر من 7 ايام, استعمال ادوية سامه للاذن لاكثرمن 7 ايام, وضع حديث الولادة في جهاز الانعاش لاكثر من 7 ايام, الوزن عند الولادة اقل من 1500 غم,والتشوهات القحفية الوجهية وبالنسب الاتية على التوالي (90,6%) (90,6%) (59,4%) (40,6%) و (21,9%).
الاستنتاجات: إن انخفاض الوزن عند الولادة والإقامة الطويلة في العناية المركزة والتهوية الميكانيكية والتسمم ألأذني للأدوية والتشوه القحفي للولدان هي عوامل الاختطار الرئيسية لفشل اختبار السمع الصوتي الناتج عن الانبعاثات
الكلمات المفتاحية: عيب السمع، فحص السمع، الولدان، الانتشار، عوامل الاختطار.