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## DWT based Identification of Amyotrophic Lateral Sclerosis using Surface EMG Signal

By Dr. Suvarna. S. Chorage & Archana Bhaskarrao Sonone

*Savitribai Phule Pune University*

**Abstract-** In the process of identification of Amyotrophic Lateral Sclerosis (ALS) which is a motor neuron disorder, extraction of feature is the most important step. In this work normal and ALS class for identification and monitoring have been included. Analysis of surface electromyography (sEMG) signal for ALS identification using discrete wavelet transform is most simple and powerful method being used all over the world. Time domain parameters, like Zero Crossing Rate (ZCR) and Root Mean Square (RMS) and frequency domain parameters like Mean Frequency (MF) and Waveform Length (WL) are considered. Threshold values for the above mentioned parameters are calculated for both the normal and ALS classes. Discrete Wavelet Transform (DWT) parameters are considered and their threshold values are also calculated for both normal and ALS classes. Surface EMG (sEMG) signal database of normal and ALS patients for both male and female is considered.

**Keywords:** ALS, sEMG, ZCR, RMS, MF, WL, DWT.

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# DWT based Identification of Amyotrophic Lateral Sclerosis using Surface EMG Signal

Dr. Suvarna. S. Chorage <sup>α</sup> & Archana Bhaskarrao Sonone <sup>σ</sup>

**Abstract-** In the process of identification of Amyotrophic Lateral Sclerosis (ALS) which is a motor neuron disorder, extraction of feature is the most important step. In this work normal and ALS class for identification and monitoring have been included. Analysis of surface electromyography (sEMG) signal for ALS identification using discrete wavelet transform is most simple and powerful method being used all over the world. Time domain parameters, like Zero Crossing Rate (ZCR) and Root Mean Square (RMS) and frequency domain parameters like Mean Frequency (MF) and Waveform Length (WL) are considered. Threshold values for the above mentioned parameters are calculated for both the normal and ALS classes. Discrete Wavelet Transform (DWT) parameters are considered and their threshold values are also calculated for both normal and ALS classes. Surface EMG (sEMG) signal database of normal and ALS patients for both male and female is considered.

**Keywords:** ALS, sEMG, ZCR, RMS, MF, WL, DWT.

## I. INTRODUCTION

Human body is made up of large number of different bundles of muscle fibers. These all bundles of fibers are arranged functionally into different motor unit which are activated by nerve impulse which is very minute electrical pulse provided by the brain's nervous systems. These electrical impulses travel through the whole length of muscle fiber spread throughout in the body. Hence very small electric currents are generated by these bundles of muscle fibers during muscle force production [1]. The electromyography (EMG) signal is an electrical responses generated by the nerve cells of the brain in the form of electrical pulses from the contraction and relaxation of bundles of muscles throughout the body. sEMG is an electrical signals associated with the uppermost layer of muscles which are the electrical impulses generated and controlled by motor nerve unit of brain [2]. sEMG consists of the information in the form of electrical impulses about the various muscle activities in the body. Obtaining sEMG signals are of two different types [3]. First method of recording sEMG is with a surface electrodes and second method is insertion needle electrode which is called as intra electrode. By applying conductive solution to the skin surface and placing the electrodes on it, sEMG recording is done. It contains important information

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about the activity of muscles, status of its health, and its characteristics. There are two types of EMG signals are 1) Surface EMG (sEMG) 2) Intramuscular EMG (iEMG) [1]. In sEMG collection of muscle contraction or expansion information from the uppermost layer of muscle .Whereas in the case of iEMG collection of information is done from the deep inside the muscles in the body. To extract information from surface EMG signal, there are different methods of different time domain, frequency domain and time-frequency domain methods have been used. EMG is very important to diagnose many nervous disorders [1]. ALS is one among those Motor Nerve Disorder (MND).ALS, which is a progressive neurodegenerative disorder that affects the muscular activities of the body because of changes in the muscle configuration [1]. The EMG represents electrical activities inside the body. As EMG signal plays very important role as diagnostic tool for the MND patients, hence extracting important information from it is very important and having vast scope in it its analysis process. To classify different MND diseases, feature extraction of sEMG is very important. Here one of those feature extraction techniques are presented based on wavelet transforms [1][3]. The rest of the paper has been arranged as, in the next section which is section II, the related work is stated. Section III explains the methodology of the identification using feature extraction. The section IV explains about the results obtained in the process and its analysis which is in the terms of discussion. In the last section V conclusion is stated.

## II. RELATED WORK

Work proposed by Shaikh Anowarul Fattah et.al [1], is based on feature extraction of EMG using discrete wavelet transform. The time domain and frequency domain features have been discussed along with discrete wavelet transform features. The time domain feature discussed in this paper is zero crossing rate and the frequency domain feature discussed is mean frequency. Wavelet transform coefficients are explained in detail. Wavelet transform used is three level decomposition coiflet transform. Accuracy of the time and frequency domain feature extraction methods are compared with wavelet transformation method.

Work done by A. B. M. Sayeed Ud Doulah et.al [2], EMG signal is studies and examined in short time fourier transform for the detection of the ALS disease.

Shapes and firing rates of motor nerve unit are the important features analyzed for the detection of neuromuscular disease. For the same study, time-frequency domain method has been considered. Use of spectrum analysis for the extraction of features has been done. The Short Time Fourier Transform method for the classification of EMG signals to detect the ALS patients and distinguish normal group.

Work done by Amol Lolure and V. R. Thool [3], is on the extraction of features from EMG and it has been evaluated in scatter graph. Extraction techniques have been applied for the recognition of hand movements. Scatter graphs which are actually mathematical diagram tool for evaluating the performance of EMG features. Mean absolute value is the key parameter has been considered which has been obtained from coefficients has shown the better performance in EMG signal analysis for hand and finger movement recognition.

Work done by Hossein Parsaei et.al [4], is the decomposition of EMG signal using the supervised technique of feature extraction. Signal decomposition techniques are discussed. Fisher discriminant analysis and supervised principal component analysis have been explored. The work proposed by the author is most beneficial in the decomposition of more complex signals. This work is quite useful for the decomposition of biomedical complex signals such as EMG in order to extract important information from them in order to detect the particular disease using the threshold values of the features.

Work done by P. Pal et.al [5], is the feature extraction for the detection of muscular atrophy. Knowledge-based expert system design and disease diagnosis is explored for the classification of EMG signal which is very hard to classify because of non stationary nature of the signal. Here on-line and off-line classification of EMG signal focusing mainly on disease diagnosis based on muscular atrophy approach.

### III. METHODOLOGIES

#### a) Discrete Wavelet Transform

Wavelet transform has been proved to be very powerful mathematical tool for biomedical signal processing as it can process non stationary time varying complex signals. Wavelet transform techniques are of two types. 1) Discrete wavelet transformation (DWT) 2) Continuous wavelet transformation (CWT). In this paper DWT has been chosen because the application is in real time engineering signal application and the biomedical signal involved here is in complex nature. In discrete wavelet transform method, it iteratively transforms interested real time signals into multi-resolution two domain subsets of coefficients of wavelet transform which contains the information about the non stationary signal which can be used to analyze the complicated

signal. Coiflet wavelet transform has been used for the decomposition of EMG signal in order to detect the neuromuscular disorder ALS. 4 level decomposition of wavelet transform has been used. Hence 5 wavelet transform coefficients are used as characteristic parameters. 4 level decomposition means signal undergoes low pass and high pass filtering 4 times to give 4 low pass filter coefficients and 1 coefficient from last stage high pass filter.

#### b) Different Features

1) *Root Mean Square (RMS)*: Time domain parameter considered is RMS which is one of the well known features in time domain for analysis of the EMG. It is defined as the square root of the arithmetic mean of the squares of a set of values. It shows the power contain in the signal. It is the most common mathematical tool for defining the effective voltage and current of a non stationary signal. Mathematically it is represented as,

$$RMS = \sqrt{\left[\frac{1}{N} \sum_{i=1}^N y_i^2\right]} \quad (1)$$

2) *Waveform length (WL)*: WL describes the complexity of non stationary EMG signal. It is defined as the cumulative length of the EMG waveform over the particular focused time period segment N where n is the number of signal samples being considered. Mathematically it is expressed as,

$$W_i = \sum_{n=1}^N |z_{n+1} - z_n| \quad (2)$$

3) *Mean Frequency (MF)*: It is defined as a pitch measure which shows the center of the distribution of power across the all frequencies in the spectrum. It represents the smooth estimation of the concentration of spectral power contain. It is a summation of all the frequencies under consideration divided by total frequencies present over the particular time segment. Mathematically it is expressed,

$$M_f = \frac{\sum f_x}{\sum f} \quad (3)$$

4) *Zero Crossing Rate (ZCR)*: Rate of sign-changes in any signal is called as ZCR. It refers the rate at which the signal crosses from positive amplitude to negative amplitude or vice a versa. In some applications only the "positive-going" or "negative-going" crossings are counted, rather than counting all the crossings. It is a summation of difference of all the present signal sample  $x(n)$  and previous signal sample  $x(n-1)$  over the particular time segment K. Mathematically it is expressed as,

$$zcr = \frac{1}{2K} \{ \sum_{n=1}^{K-1} |sgn[x(n)] - sgn[x(n-1)]| \} \quad (4)$$

5) *DWT Coefficients*: 4 level decomposition is been used in coiflet wavelet transformation for feature extraction to get 5 coefficients in all, 4 from 4 level low pass filter and 1 from last stage high pass filter such as

cd1,cd2,cd3,cd4 and ca4. The energy contain in the above said coefficients is been used in order to use them as features for detecting the neuromuscular disorder.

6) *KNN Classifier*: It is k-nearest neighborhood algorithm (KNN). It is used for classification of objects in pattern recognition which is based on closest training examples. It is an instant based learning or lazy learning. In this paper for the classification of sEMG into two classes normal and defected i.e. ALS KNN is used.

#### IV. RESULTS AND DISCUSSIONS

EMG database of 30 normal male and 15 normal females of age between 22 to 35 and 40 to 67 having normal body shape is been considered. For ALS patients also 30 male and 15 female EMG database is been considered. The features on the basis of which detection of ALS and classifying them into two group of normal class and ALS class are considered as follow. Mean frequency which is the frequency domain feature showing the comparison between normal and ALS class. Here the bubbled line shows the graph for normal person and plain line shows the graph for ALS patient. Following graph shows the MF in normal person is more stable as compares to ALS person. MF is more for ALS patient than normal. But this frequency domain parameter does not give us accuracy in every case. Hence for more accurate results we are exploring the other techniques.

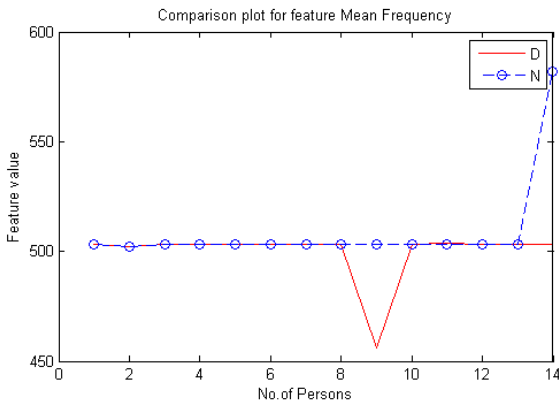


Fig. No. 1: Comparison graph for Mean Frequency in normal (Bubbled line) and ALS patient (Plain line).

Another frequency domain feature we considered is waveform length which is denoted as WL and which refers the complexity of the waveform in the particular time segment. Following graph shows the graph of WL for both normal and ALS person. WL is more in ALS than that of normal persons.

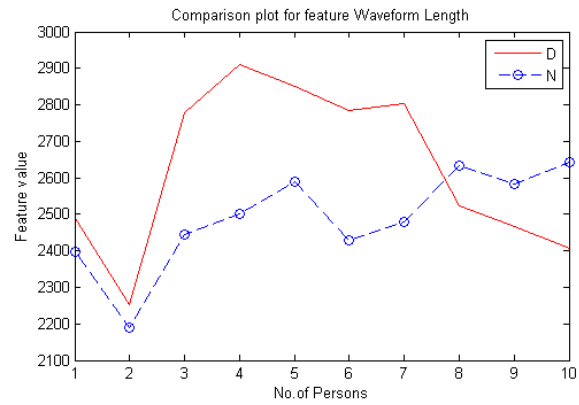


Fig. No. 2: Comparison graph for Waveform Length in normal (Bubbled line) and ALS patients (Plain).

Time domain feature Root Mean Square has been considered to show the time domain parameter in normal and ALS patients. Following graph shows the comparison between normal and ALS patient. RMS value is always greater in ALS than normal person.

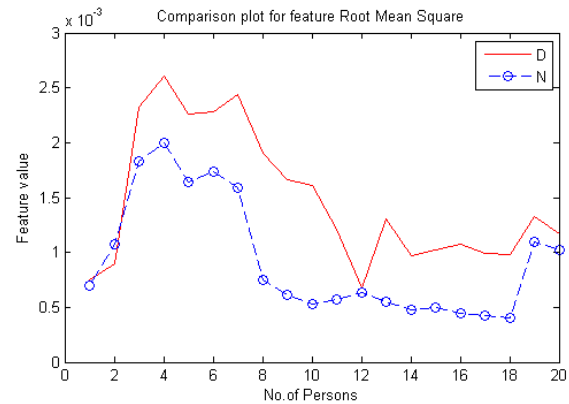


Fig. No. 3: Comparison graph for RMS in normal (Bubbled line) and ALS patients (Plain line)

Another time domain parameter we considered here is Zero crossing rate for both the class. ZCR is greater in ALS than that of in normal persons. Following graph shows the comparison for ZCR between normal and ALS patients.

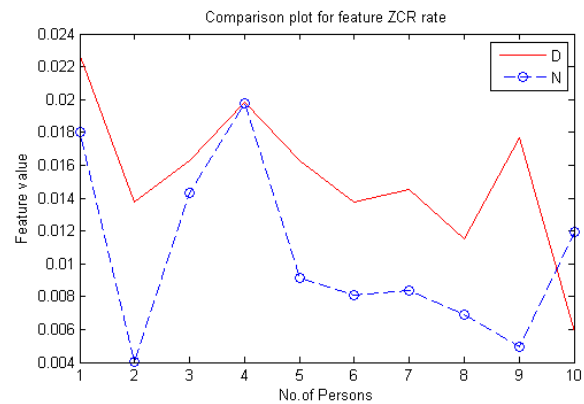


Fig. No.4: Comparison graph for Zero Crossing Rate in normal (Bubbled line) and ALS patients (plain line).

As only frequency domain or time domain parameter does not give accurate identification of ALS. Hence we exploring the other techniques which give the multi-dimensional parameter to get the more accurate results. Following graphs show the energy of wavelet transform coefficients for 4level decomposition which gives us 5 coefficients are as follows. D1,D2,D3,D4 and C4 these are wavelet transform coefficients obtained from 4level decomposition wavelet transform from which D1,D2,D3 and D4 are obtained from low pass filter and last coefficient C4 is obtained from last stage high pass filter.

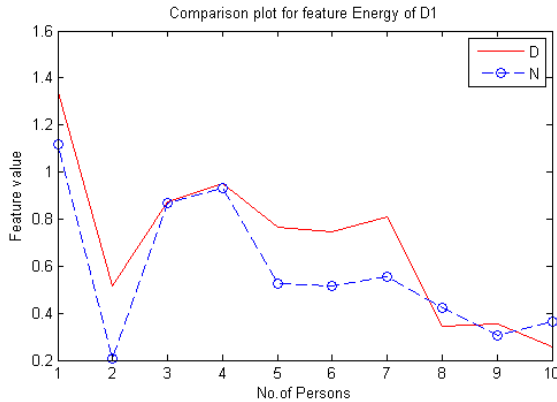


Fig. No. 5: Comparison of energy of D1 coefficient in normal (Bubbled line) and ALS patients (Plain line).

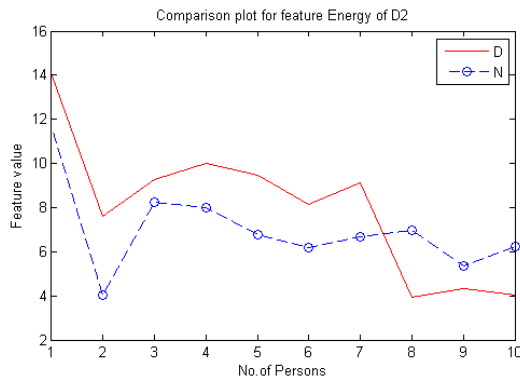


Fig. No. 6: Comparison of energy of D2 coefficient in normal (Bubbled line) and ALS patients (Plain line).

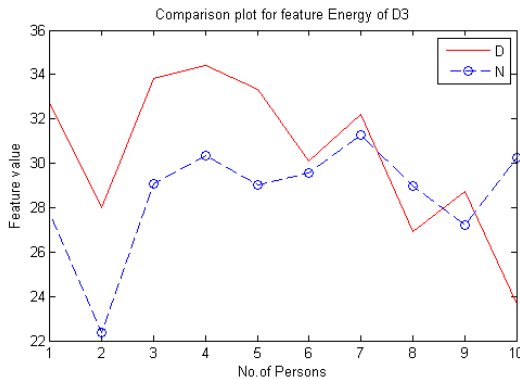


Fig. No. 7: Comparison of energy of D3 coefficient in normal (Bubbled line) and ALS patients (Plain line).

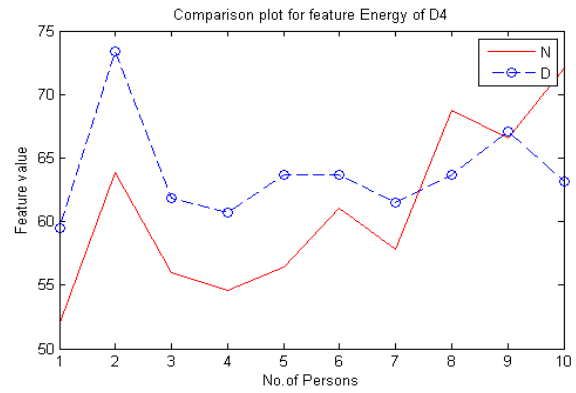


Fig. No. 8: Comparison of energy of D4 coefficient in normal (Plain line) and ALS patients (Bubbled line).

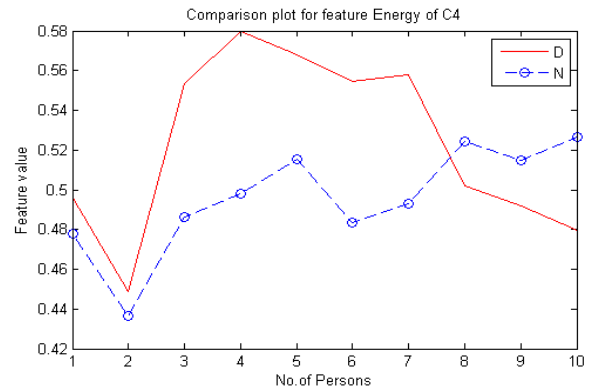


Fig. No. 9: Comparison of energy of C4 coefficient in normal (Bubbled line) and ALS patients (Plain line).

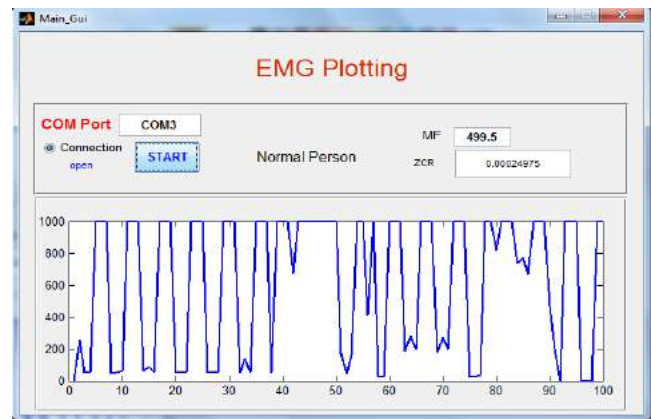


Fig. No. 10: GUI showing the result of normal person EMG taken from EMG sensor of hardware part of the project along with its mean frequency (MF) and zero crossing rate (ZCR).

In figure No.10 mean frequency of normal person's EMG is less than 500 and zero crossing rate is 0.002464 which is nearly to the values obtained from the signals of database used for normal persons. In figure No.11 MF and ZCR are zero as no signal is detected by the EMG sensor. This case can be obtained in two different ways first when the person whose EMG is to be taken is dead and secondly when EMG sensor is not connected.



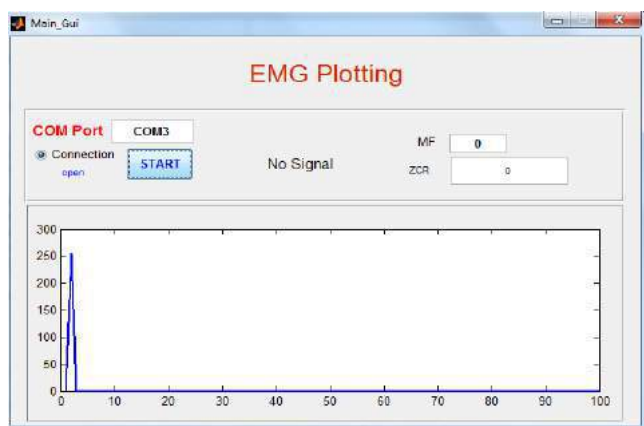


Fig. No. 11: GUI showing the results when there is no signal is detected by the EMG sensor and value of both MF and ZCR are zero.

## V. CONCLUSION

To identify the ALS disease on the basis of feature extraction from the sEMG database we have used the 4level decomposition wavelet transform to get the multi-dimensional resolution of higher accuracy than the conventional time and frequency domain analysis. From the time domain, frequency domain and wavelet domain feature extraction, we compare the threshold values for the different parameters in above mentioned domains to identify the ALS patient with more accuracy. Characteristic table of features in different domains and their values in normal and ALS are shown as follows.

Table No. 1: Threshold values for the normal and ALS patients

Sr. No.	Parameter Name	Threshold Values in normal	Threshold Values in ALS
1.	Mean Frequency	502	503
2.	Waveform Length	2535	2750
3.	Root Mean Square	1.525	2.575
4.	Zero Crossing Rate	0.010	0.0114
5.	Energy of D1	0.5125	0.875
6.	Energy of D2	7.120	9.70
7.	Energy of D3	30.5	31.6
8.	Energy of D4	59.9	63.2
9.	Energy of C4	0.496	0.483

## VI. ACKNOWLEDGMENT

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## Lung Cancer Screening: Beliefs and Recommendations of Primary Care Physicians at the National Guard Hospital (NGHA)

By Roaa R Amer, Adel F Yasky & Alia H Zawawi

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**Abstract- Background:** Early detection of lung cancers via screening may aid in decreasing the associated mortality; however, optimal screening methods have not yet been established.

**Objectives:** We aimed to explore the beliefs and attitudes of primary care physicians (PCPs) towards lung cancer screening guidelines in asymptomatic patients.

**Methods:** We conducted a cross-sectional descriptive study at the NGHA primary care centres, using a validated questionnaire, with 11 questions, developed by the National Cancer Institute, USA, and customized to our medical settings.

**Results:** 37% of family physicians requested chest X-rays; 1.9%, sputum cytology; and 3.7%, low-dose spiral chest computed tomography (CT) scans. Of the internists, 42.1% requested low-dose CT scans; 62.5%, chest X-rays; and 5%, sputum cytology. The mean knowledge scores for family physicians and internists regarding screening guidelines were 2.3 and 1.5, respectively, and those for their belief in the effectiveness of screening modalities were 7.6 and 6.6, respectively.

**Keywords:** lung cancer, physicians, belief and recommendations of PCPs, screening guidelines, family medicine, internal medicine, asymptomatic.

**GJMR-F Classification:** NLMC Code: QZ 206



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# Lung Cancer Screening: Beliefs and Recommendations of Primary Care Physicians at the National Guard Hospital (NGHA)

Roaa R Amer <sup>α</sup>, Adel F Yasky <sup>σ</sup> & Alia H Zawawi <sup>ρ</sup>

**Abstract Background:** Early detection of lung cancers via screening may aid in decreasing the associated mortality; however, optimal screening methods have not yet been established.

**Objectives:** We aimed to explore the beliefs and attitudes of primary care physicians (PCPs) towards lung cancer screening guidelines in asymptomatic patients.

**Methods:** We conducted a cross-sectional descriptive study at the NGHA primary care centres, using a validated questionnaire, with 11 questions, developed by the National Cancer Institute, USA, and customized to our medical settings.

**Results:** 37% of family physicians requested chest X-rays; 1.9%, sputum cytology; and 3.7%, low-dose spiral chest computed tomography (CT) scans. Of the internists, 42.1% requested low-dose CT scans; 62.5%, chest X-rays; and 5%, sputum cytology. The mean knowledge scores for family physicians and internists regarding screening guidelines were 2.3 and 1.5, respectively, and those for their belief in the effectiveness of screening modalities were 7.6 and 6.6, respectively.

**Conclusion:** To harmonize lung cancer screening guidelines with clinical practice, further research on factors influencing the perceptions and responses of PCPs to screening guidelines needs to be conducted.

**Keywords:** lung cancer, physicians, belief and recommendations of PCPs, screening guidelines, family medicine, internal medicine, asymptomatic.

## I. INTRODUCTION

Worldwide, lung cancer is considered fatal. Early detection via screening may aid in the decrease of cancer-related mortality rate. Till date, the optimal method for lung cancer screening is controversial (Nanavaty et al, 2014). However, regardless of these controversies, due to the lack of sufficient evidence, major medical experts and recent guidelines do not recommend screening in asymptomatic patients, even in those have histories of heavy or long-term smoking (Lung Cancer: Screening - US Preventive Services Task Force, 2013; NCCN Guidelines for Patients® | Lung Cancer Screening, 2016; Lung Cancer Screening Guidelines, Cancer.org. 2016; Care, 2015). Due to the increasing incidence of

lung cancer in Saudi Arabia, primary care physicians (PCPs) should have significant roles in preventing lung cancers and identifying those who are at risk; the choice of appropriate tools and candidates for screening is very crucial. The aim of this study is to explore the beliefs and attitudes of PCPs, towards lung cancer screening guidelines, in asymptomatic patients.

## II. METHODS

A cross-sectional descriptive study was conducted at the National Guard Hospital (NGHA), Riyadh between January February 2017, using the validated lung cancer screening questionnaire developed by the National Cancer Institute (NCI), USA, in collaboration with the Agency for Healthcare Research and Quality, and the Centers for Disease Control and Prevention, USA. The questionnaire was edited and customized, by adding and eliminating questions, to be compatible with our medical setting.

All 146 PCPs, including family physicians and internists, were included in the study, without sampling. A pilot study was conducted on 10 physicians to ensure full comprehension of the questionnaire; this resulted in some modifications in vocabulary and format to avoid ambiguity. The King Abdullah International Medical Research Center (KAIMRC) also reviewed the survey tool. This contains questions related to the knowledge, attitudes, and demographics of the physicians, and takes approximately 10 minutes to complete.

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) software version 20.0. Frequencies and percentages were utilized to represent categorical variables, and the Chi-square test was used to investigate the relationship between variables. The knowledge scores were marked as follows: correct answers were marked with 1, and wrong answers, with 0. The sum of all knowledge questions was calculated for each participant. The knowledge scores were computed based on 11 questions from the questionnaire, and the answers were evaluated according to the guidelines mentioned in Figure 1.

The attitude scores were marked as follows: answers with positive attitude were marked with 1, and negative attitude, with 0. The sum of all attitude

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questions was calculated for each respondent. Attitude scores were computed based on 8 questions. The means of these scores were compared between groups, using the Student's t-test. P-values of 0.05 or less were considered significant. Permission for conducting the study was obtained from KAIMRC in Riyadh. The cover sheet of the questionnaire explained that the physicians participated voluntarily in the study, and this was considered as consent. All data was treated anonymously.

51%) and internal medicine (response rate, 48.7%) departments, participated in the study. The mean knowledge scores for the internists and family medicine physicians, regarding their belief in the effectiveness of the different screening modalities in reducing the lung cancer-related mortality in asymptomatic patients were 6.6 and 7.6 (P-value=0.54), respectively. The results of the first question on the questionnaire are shown in table-1.

### III. RESULTS

A total of 74 PCPs (total response rate, 50.68%), including those from family medicine (response rate,

**Table 1:** Responses of family physicians and internists on the modality of choice for lung cancer screening per case

		Never smoked		Former smoker		Current smoker	
Very Effective Modality							
Chest X-ray	IM	5.26%	P-Value	10.4%	P-Value	21.05%	P-Value
	FM	7.27%	0.7635	9.09%	0.8538	27.27%	0.5926
Sputum Cytology	IM	0%	P-Value	5.26%	P-Value	21.05%	P-Value
	FM	0%	-	1.1%	0.4247	14.5%	0.5071
Low-dose CT	IM	26.31%	P-Value	57.89%	P-Value	57.89%	P-Value
	FM	14.4%	0.2451	30.9%	<b>0.0245</b>	55.96%	0.908
Somewhat Effective modality							
Chest X-ray	IM	36.84%	P-Value	42.1%	P-Value	42.1%	P-Value
	FM	18.18%	0.0955	36.36%	0.6564	32.27%	0.4604
Sputum Cytology	IM	42.10%	P-Value	47.36%	P-Value	36.84%	P-Value
	FM	18.18%	<b>0.0361</b>	31.1%	0.1951	27.25%	0.43%
Low-dose CT	IM	15.8%	P-Value	5.26%	P-Value	5.26%	P-Value
	FM	12.72%	0.8955	23.63%	0.0779	7.19%	0.7635
Not Effective Modality							
Chest X-ray	IM	52.63%	P-Value	42.1%	P-Value	36.85%	P-Value
	FM	72.72%	0.1067	47.45%	0.6968	36.63%	0.9702
Sputum Cytology	IM	52.63%	P-Value	42.1%	P-Value	36.84%	P-Value
	FM	70.82%	0.1464	51.7%	0.508	49.17%	0.3557
Low-dose CT	IM	47.36%	P-Value	36.85%	P-Value	36.85%	P-Value
	FM	65.65%	0.2131	38.2%	0.8079	35.25%	0.8565

Do not Know the Effectiveness of Modality							
Chest X-ray	IM	5.27%	P-Value	5.4%	P-Value	0%	P-Value
	FM	1.83%	0.4247	7.1%	0.7635	36.63%	<0.001
Sputum Cytology	IM	5.27%	P-Value	5.28%	P-Value	5.27%	P-Value
	FM	1.83%	0.4685	16.1%	0.2223	9.08%	0.5982
Low-dose CT	IM	10.53%	P-Value	0%	P-Value	0%	P-Value
	FM	7.23%	0.6542	7.27%	<0.001	1.6%	<0.001

IM: Internal Medicine, FM: Family medicine, CT: computed tomography. P-value<0.05 is considered significant.

The mean knowledge scores for family and internal medicine physicians regarding lung cancer screening guidelines were 2.3 and 1.5 (P-value=0.48), respectively. The knowledge of the physicians,

regarding the various lung cancer screening guidelines for asymptomatic patients with histories of smoking less than 30 packs per year, or for those who have never smoked is illustrated in figure-1.

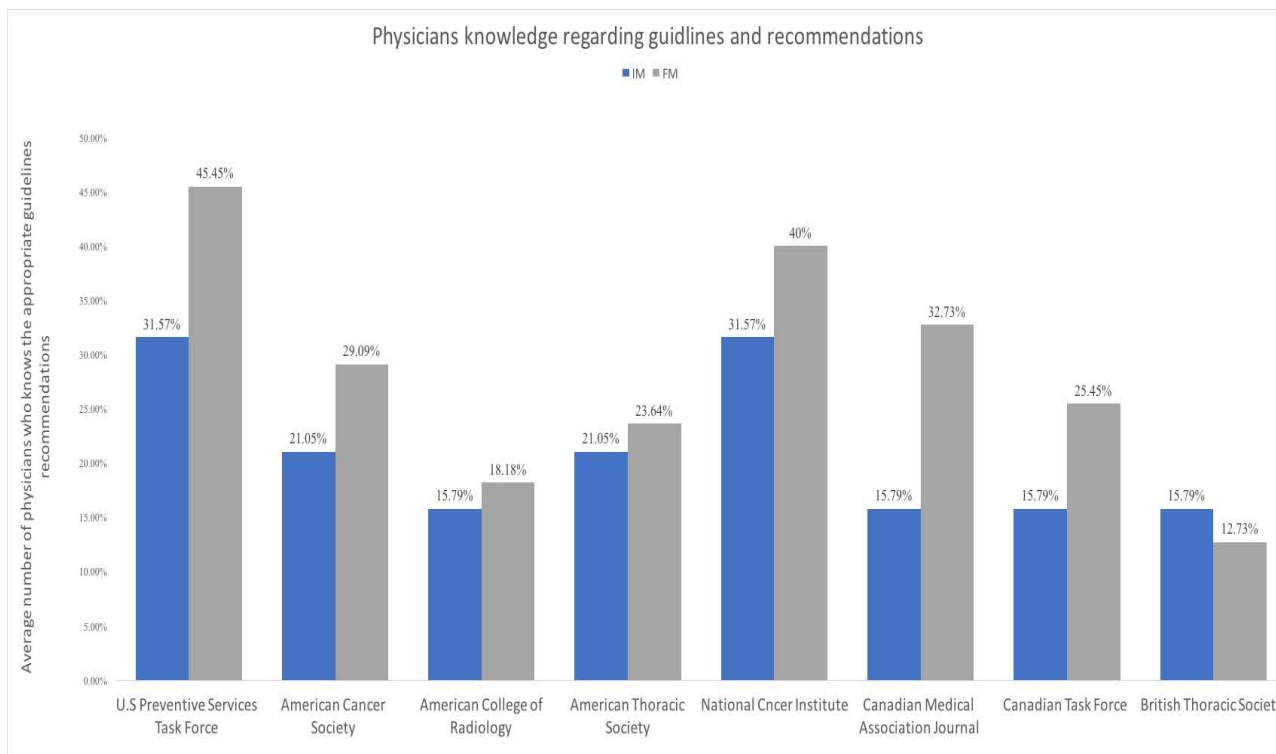


Figure 1: Physicians knowledge regarding lung cancer screening guideline and recommendation

The second question included various scenarios where the physicians were asked to choose the best lung screening modality, with the assumptions that the patients had not been previously screened, did not have any symptoms of lung cancer, did not express any preferences for lung screening, either in general or using a specific modality, and had no occupational exposure to known or suspected lung carcinogens. The responses to the second question are demonstrated in figure-2.





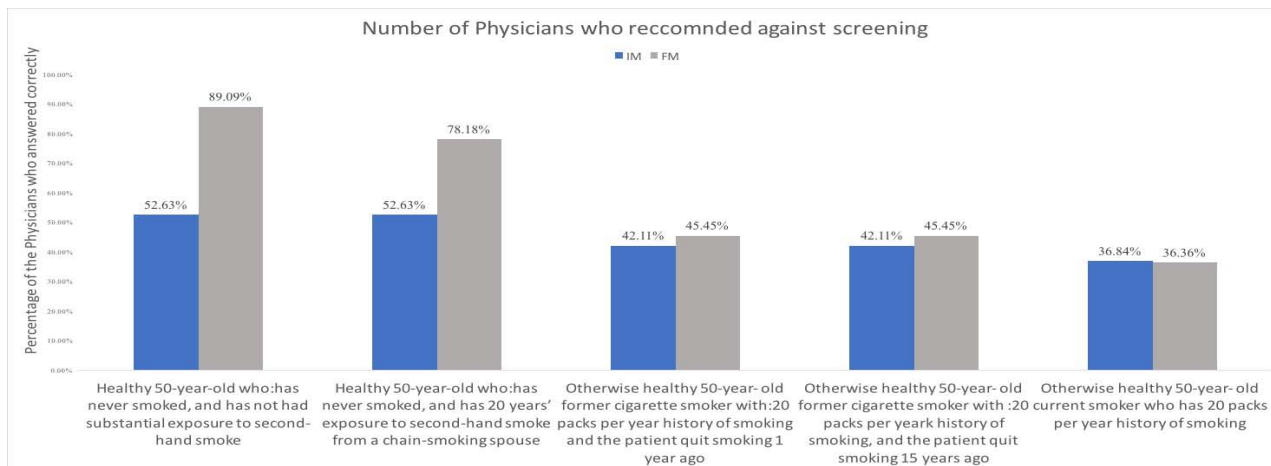


Figure 2: Responses by the physicians to question 2, with the assumptions that these patients had not been previously screened for lung cancer, did not have symptoms of lung cancer, did not expressed any preference for screening, either in general or with a specific modality, and had no occupational exposure to known or suspected lung carcinogens

According to their practice, 37% of family physicians requested chest X-rays, 1.9%, sputum cytology, and 3.7%, low-dose spiral chest computed tomography (CT) scans for lung cancer screening of asymptomatic patients in the past 12 months (figure-3).

Additionally, of 19 internists, 62.5% requested chest X-rays, 5%, sputum cytology, and 42.1%, low-dose spiral CT scans for lung cancer screening of asymptomatic patients in the past 12 months (figure-3).

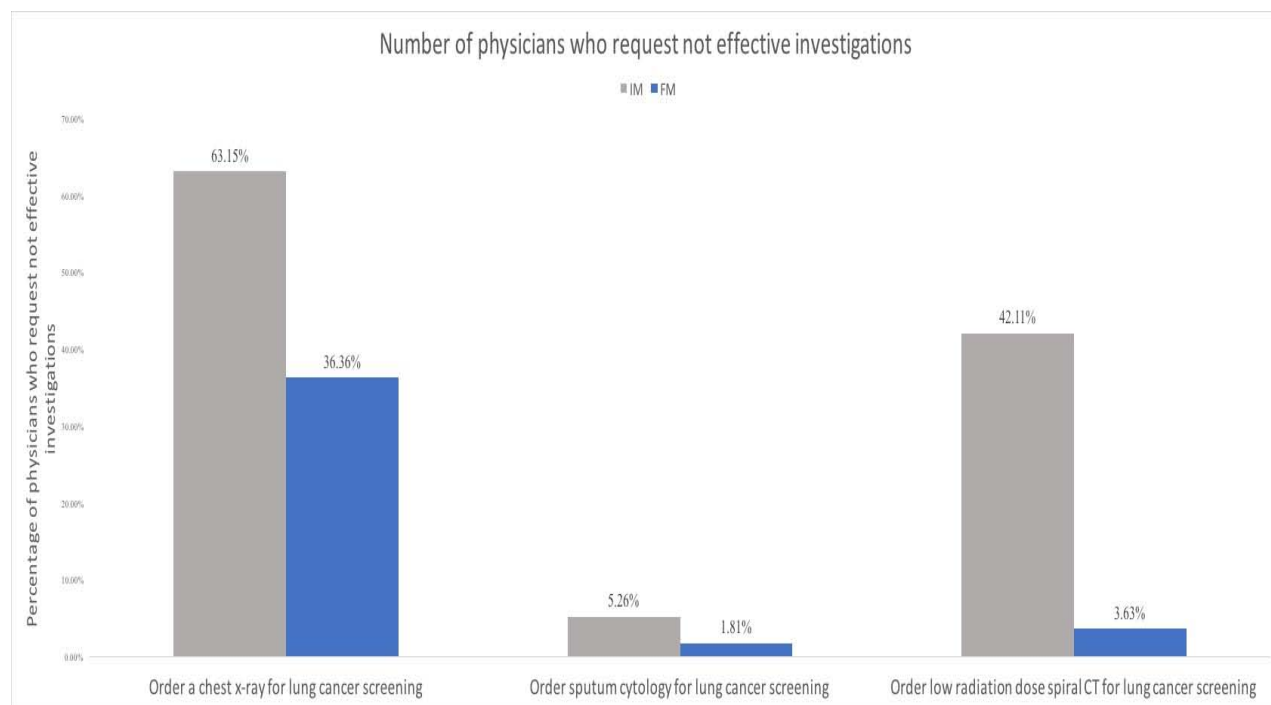


Figure 3: The practice of physicians toward clinical screening tools for lung cancer

The average percentage of time spent by family physicians in providing medical care was 81.73%; in research, 8.18%; teaching, 9%; and others, 1.09% (administration, higher education, etc.). The average percentage of time spent by internal medicine physicians in providing medical care was 80.52%; research, 12.1%; and teaching, 7.38%. The average number of patients treated during a typical week by our

family or internal medicine physicians is demonstrated in figure-4, and the mean age groups of patients seen per specialty are shown in figure-5.

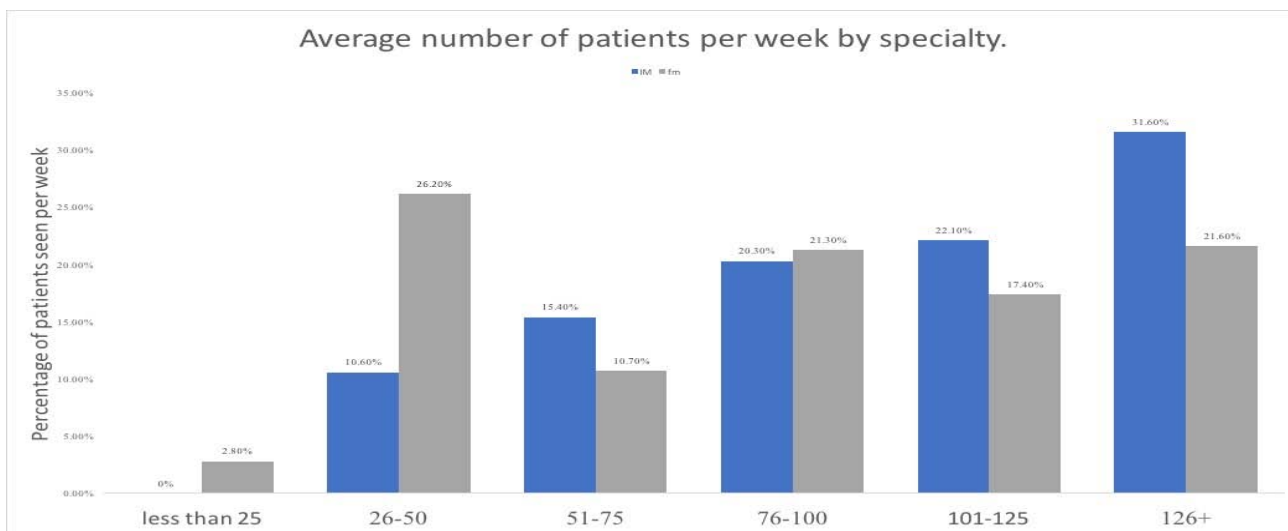


Figure 4: Percentage of patients seen by physicians per week

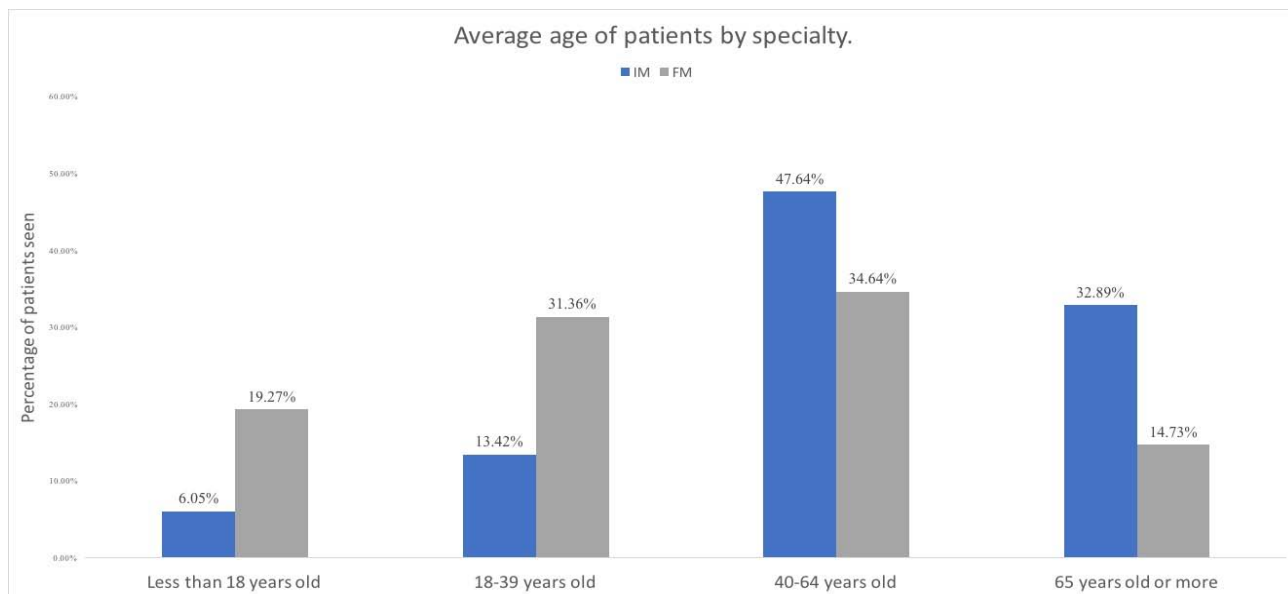


Figure 5: Average of patients' age according to specialty

#### IV. DISCUSSION

Worldwide, lung cancer is considered fatal, with a 5-year survival rate of 16% in the United States (Dela Cruz et al, 2011; Alamoudi, 2010). During 2013, 2,125,844 new cases of lung cancer were diagnosed in the United States, and over 156,176 patients died (Fact Sheets by Cancer. Globocan.iarc.fr. 2016). In the United Kingdom, 34,000 new cases are documented annually (Spiro et al, 2005). According to the latest Saudi National Cancer Registry, 397 cases were diagnosed in 2010, accounting for 4% of cancers (King Faisal Specialist Hospital & Research Centre - Centers of Excellence - Cancer Centre. Telemedicine.kfshrc.edu.sa. 2016).

Early detection of lung cancer via screening is greatly expected to aid in decreasing the mortality rate. The optimal method for lung cancer screening has not

yet been established (Nanavaty et al, 2014). However, regardless of these controversies, due to lack of sufficient evidence, major medical experts and recent guidelines do not recommend screening in asymptomatic patients, even if they have histories of heavy or long-term smoking (Lung Cancer: Screening - US Preventive Services Task Force, 2013; NCCN Guidelines for Patients® | Lung Cancer Screening, 2016; Lung Cancer Screening Guidelines, Cancer.org. 2016; Care C, 2015).

Furthermore, a similar study conducted in 2012 in the United States aimed to explore the beliefs and attitudes of PCPs regarding lung cancer screening. The results showed that one-fourth of all PCPs recommended screening in asymptomatic patients, and one-half requested chest radiographs (Klabunde et al, 2012). In 2010, another study showed similar results; it

was found that the beliefs of many PCPs regarding lung cancer were inconsistent with the current guidelines and recommendations (Klabunde et al, 2010).

The findings of this study were consistent with existing research and theoretical evidence, which suggests a progressive increase in the incidence of lung cancer in Saudi Arabia, and indicates the challenges encountered in the timely recognition of lung cancer. The research indicated that the average knowledge of family physicians regarding lung cancer screening guidelines was minimal, although they reported a score of 6.6 with respect to their beliefs about the importance of lung cancer screening, and between practice and beliefs with a score of 2.2. This trend continues, despite recommendations by numerous organizations for lung cancer screening.

Previous research has determined that the recommendations by physicians are important predictors of health-seeking behaviour in patients (Dela Cruz et al, 2011). Limited knowledge of the guideline recommendations is likely to inhibit physicians from facilitating collective decision-making conversations, concerning the possible advantages, uncertainties, and disadvantages of lung cancer detections, when interacting with their patients (Spiro et al, 2005, National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. [Healthcaredelivery.cancer.gov](http://Healthcaredelivery.cancer.gov). 2016).

The results indicated that internal medicine physicians had knowledge scores of 1.5, regarding lung cancer screening guidelines. The findings of this investigation are in agreement with a previous survey in 2011 that examined lung cancer screening practices (Lung Cancer Screening (PDQ®)–Health Professional Version. National Cancer Institute. 2016). The survey illustrated that family physicians have higher preferences for requesting chest radiographs in asymptomatic patients with lung cancer, compared to internists.

The research findings showed that the lung cancer screening recommendations and beliefs of many PCPs were inconsistent with current evidence and guidelines. The study considered the key modalities that have been utilized in lung cancer screening, which include chest X-rays, low-dose CT scans, and sputum cytology. Most internists believe that low-dose CT is efficient in decreasing lung cancer mortalities among current smokers; this concurs with the assertion of previous researchers (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. [Healthcaredelivery.cancer.gov](http://Healthcaredelivery.cancer.gov). 2016; Lung Cancer Screening (PDQ®)–Health Professional Version. National Cancer Institute. 2016). Those physicians who had completed medical school more than 15 years ago were more likely to request for chest radio graphs for lung cancer detection. These results concur with physician beliefs concerning screening. Senior

physicians appear to request the specific lung cancer detection method that is compatible with their prior medical training (Humphrey et al, 2013).

The results show that the demands of patients are related to the physician reports regarding requests for lung cancer detection, and concur with previous studies demonstrating that the requests of patients affect the physician ordering a test for cancer susceptibility. Physician evaluations linked with lung cancer detection might aid in targeting the involvement of physicians that are in dire need of information and evidence regarding lung cancer detection guidelines (Mazzone et al, 2015). Most PCPs (89.09%) acknowledged that they recommended against screening in patients who were over 50 years of age, who had never smoked, or who did not have substantial exposure to passive smoking, but only 36.36% of PCPs recommended against screening for lung cancer in patients who were either former or current smokers, including those exposed to passive smoking.

We analysed physician preferences for the best screening modalities for patients that have not been previously screened, have no symptoms of lung cancer, have not expressed a preference for lung cancer screening, either in general or with a specific modality, and have not had any prior exposure to known or suspected lung carcinogens. The results demonstrated that 37% of family physicians requested chest X-rays; 1.9%, sputum cytology; and 3.7%, low-dose spiral chest CT scans, for lung cancer detection. However, among the internists, 42.1% requested low-dose CT scans for lung cancer detection; 62.5%, chest X-rays; and 5%, sputum cytology. From the above results, it appears that primary care physicians in the King Abdulaziz Medical City (KAMC) primary care centre have not decreased the practice of requesting chest X-rays to detect lung cancers in asymptomatic individuals.

Nonetheless, among PCPs who recommend the screening of patients for lung cancer, 63.15% of internists and 36.36% of family physicians recommend the use of chest X-rays, which is not a recommended test (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. [Healthcaredelivery.cancer.gov](http://Healthcaredelivery.cancer.gov). 2016). This result is consistent with the previous understanding of the national provider, to examine lung cancer screening practices before launching the NCI guidelines. About 26.31% of internal medicine physicians viewed low-dose CT as an effective screening modality, compared to 14.4% of family physicians. The propensity of PCPs to suggest a particular screening technique increases with the exposure of the patient to smoking.

The knowledge of guidelines was not associated with the utilization of low-dose CT; surprisingly, despite only 31.5% of internists knowing the NCI, compared to 40% of family physicians, the use of

low-dose CT scans was the highest among the internists. The use of chest-X-rays is partly accredited to concerns about financial costs, the unavailability of other screening modalities, and lack of insurance coverage (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). The small percentage (13.01%) of all PCPs who possessed lung screening programs or aids in their work setting may be attributed to the slow uptake of low-dose CT, and the increased usage of chest X-rays becoming more common due to extensive coverage. Nevertheless, the National Lung Screening Trial (NLST) presents evidence that lung cancer detection with low-dose CT is more efficient than with other commonly performed screening interventions, such as sputum cytology and chest X-rays (Lung Cancer Screening (PDQ®)–Health Professional Version. National Cancer Institute. 2016).

The research findings have shown the beliefs of PCPs concerning practice guidelines, test effectiveness, and tendency to intensify for any cancer that is highly related to the lung cancer screening recommendations. They substantiate an earlier, but much smaller study, which suggests that aggressive cancer screening by family physicians is related to their beliefs (Alamoudi, 2010).

The requests by PCPs for unverified lung cancer screening techniques have various implications. One such implication is the potential psychological harm that results from false-positive or false-negative results (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). Physical damage can also result from unwarranted invasive procedures that are undertaken as follow-up for false-positive screening (Klabunde, 2012). The use of unrecommended lung cancer technologies will eventually drive up health care costs. According to the data from the NLST, an average of 30% of patients who undergo low-dose CT scanning as a detection procedure will have at least one false-positive screening (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). Moreover, three of every 1,000 persons screened are estimated to develop major complications associated with the procedure, and three-to-five people may be over-diagnosed with lung cancer (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). There is a need for current and future refinements in screening; for instance, raising the threshold for a "positive" result of screening in the national guidelines, and adopting calculators to predict

the likelihood of lung cancer, which will help lower the false-positives rate (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). The results from this study showed that PCPs had glaring gaps in their knowledge of lung cancer screening; this screening tends to happen opportunistically rather than through well-organized programs (Lung Cancer Screening (PDQ®)–Health Professional Version. National Cancer Institute. 2016; Klabunde, 2010). This, in turn, may result in a considerable percentage of incorrectly screened adults, unless intensive efforts are made to notify PCPs of the proper explanation of the NLST results, and better screening approaches in clinical practice.

The study suggests that only 35% of PCPs promote lung cancer screening by initiating conversations with the patients regarding the advantages and risks of undertaking such screening; this limited number results from the lack of familiarity with the clinical practice guidelines for lung cancer detection. The existing evidence does not support screening for asymptomatic patients, not with standing their exposure to smoking (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. Healthcare delivery.cancer.gov. 2016). This may be because being attuned to the current practice guidelines can be a daunting task for physicians (Klabunde, 2010). The proliferation of several guidelines may negatively affect the ability of PCPs to adhere to them. The use of an academic detailing approach may encourage supportive attitudes and beliefs towards lung cancer screening, as well as, inspire disease advocacy groups, and the encourage the availability of technology that facilitates screening (Nanavaty et al, 2016).

*Strengths and limitations:* A major strength of this study was the extent of evidence available in literature regarding the research objectives. The results reflect the views of both inexperienced and experienced providers with diverse clinical understanding, from the two predominant fields of primary care services, namely, family medicine and internal medicine.

A limitation of the study is based on the attitudes, recommendations, and practices of physicians; these were obtained through a self-reported questionnaire that was not verified using any other sources, such as medical claims or reports. To reduce the workload of the respondents, the survey questionnaire on lung cancer detection was comparatively short, and it did not have the capacity to extract details about specific features of the patients for whom the PCPs had requested lung cancer screenings, and their extent and type of smoking exposure. Moreover, the study relied on PCP accounts of screening behaviour, which are subject to recall bias or



social desirability. Lastly, the low response rate (51%) did not allow generalization of the results of the study to other primary care centres in Riyadh and Saudi Arabia.

## V. CONCLUSION

Additional research is warranted to educate PCPs and health care consumers, concerning the need, evidence base, guidelines, cost, and potential risks, of lung cancer screening guidelines. The public has an exaggeratedly positive view of cancer detection, albeit with an inadequate understanding of the potential damage. The utilization of CT scans is rising rapidly in KAMC primary care centres. There is a need to address current barriers, such as, insurance coverage, financial cost, frequency of false-positive results, and associated complications with screening.

These initiatives will be essential in providing PCPs with the necessary knowledge to make decisions regarding lung cancer screening (National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. [Healthcaredelivery.cancer.gov](http://Healthcaredelivery.cancer.gov). 2016). These pertinent concerns, in conjunction with study findings and developing an evidence base, highlight the significance of continuously monitoring the knowledge, practices, and beliefs of PCPs, as these are inter connected with lung cancer detection. Further research is required to enumerate the factors influencing the perceptions and responses of PCPs, regarding lung cancer screening guidelines, to enhance the current understanding of these guidelines.

The present study uncovers the disconnect that exists amid evidence and practice in lung cancer detection, and explores critical background for reflection on the results of the significant and extremely publicized NSLT (Lung Cancer Screening (PDQ®)–Health Professional Version. National Cancer Institute. 2016). Most of the guidelines are very specific to people aged between 50–75 years, who are either current smokers or were heavy smokers with histories of smoking a minimum of 30packs per year(National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening. [Healthcaredelivery.cancer.gov](http://Healthcaredelivery.cancer.gov). 2016). Therefore, any alteration in the screening commendations would only apply to this select and high-risk population. Lung cancer screening is established concept in Saudi Arabia, and the information regarding the usage of lung cancer screening in Saudi Arabia is quite limited and is confined to the national data sources, which provide population estimates of cancer screening. There is a need to harmonize lung cancer screening guidelines and clinical practice.

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## Peribulbar Blocks: The Experience of a Specialized Ophthalmologic Surgery Centre

By Daniel Rodrigues Alves, Inês Baltazar, Juliana Alves, Teresa Almeida, Dulce Santos  
& Henriqueta Abreu

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**Methods:** We performed a retrospective analysis of the anaesthetic register of patients undergoing peribulbar blocks for different ophthalmic procedures over a 9 months period, describing its safety, effectiveness and using logistic regression to identify possible factors influencing block quality.

**Results:** In a total of 309 blocks there were 9 minor complications, none of which produced lasting consequences. Variables affecting sensory block depth were type of sedation during the block procedure, volume of local anaesthetic administered and type of surgery.

**Mesh Keywords:** *anesthesia, regional – nerve block – eye – ophthalmologic surgical procedures.*

**GJMR-F Classification:** NLMC Code: WW 168



*Strictly as per the compliance and regulations of:*



# Peribulbar Blocks: The Experience of a Specialized Ophthalmologic Surgery Centre

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& Henriqueta Abreu <sup>§</sup>

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**Results:** In a total of 309 blocks there were 9 minor complications, none of which produced lasting consequences. Variables affecting sensory block depth were type of sedation during the block procedure, volume of local anaesthetic administered and type of surgery.

**Conclusion:** Peribulbar blocks appear to have a favourable safety profile, but the rarity of serious complications makes it difficult to correctly assess their incidence. Even though block depth was appropriate in most situations, there is still room for improvement, namely by optimizing both the volume of local anaesthetic administered and sedation for the block procedure.

**Mesh Keywords:** *anesthesia, regional – nerve block – eye – ophthalmologic surgical procedures.*

**Table 1:** Some cases where general anaesthesia is usually considered for Ophthalmic surgeries

- Children
- Patients unable to cooperate either psychologically or due to communication problems
- Intense tremor or nystagmus
- Perforating eye injury
- Blindness in the non-operated eye (relative)
- Persistent cough
- Inability to tolerate the recumbent position
- Contraindication to other techniques, such as allergy to local anaesthetics
- Cases of block failure despite adequate supplementation

Of course not all techniques are adequate for all types of surgery, but unfortunately there is no up-to-date

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## I. INTRODUCTION

We've come a long way since the performance of the first invasive treatments for cataracts, dating back to the fifth century BC in India<sup>1</sup>. Nowadays, a whole range of Ophthalmologic procedures is available to treat many of the ailments once leading to inevitable blindness, in part boosted by the development of Anaesthesiology.

In striking opposition to what happened just a few decades ago, in most centers general anaesthesia is now seldom performed for ophthalmic surgery in mentally capable adults<sup>2</sup> (Table 1). Local and regional techniques allow not only avoidance of general anaesthesia in typically elderly patients with multiple comorbidities<sup>2,3</sup>, but also to take advantage of the faster recovery time loco-regional techniques allow<sup>4,5</sup>, which is particularly relevant when we consider the ambulatory setting usually involved. Many different options are available, be them topical anaesthesia, sub conjunctival anaesthesia, sub-Tenon's blocks, peribulbar blocks or retrobulbar blocks.

in each case<sup>2,6</sup>, making practice differ considerably between institutions. In the current era of Medicine, where litigation is ever-increasing and feared, many professionals have now shifted their preference to topical anaesthesia with mild sedation whenever possible, as it perverts normal physiology the least and does not appear to be significantly associated with direct harm. After all, even though ophthalmic block complications (Table 2) are rare<sup>7</sup>, the risk is real<sup>5,8-12</sup>, and the severity of potential consequences makes them the most frequent disabling injuries related to regional

anaesthesia reported in the ASA Closed Claims Project database<sup>10, 13</sup>, with retrobulbar blocks<sup>14</sup> in particular responsible for 38% of total permanent / disabling injuries in this part of the register.

*Table 2:* Some risks subsequent to eye blocks

- Ocular perforation
- Direct optic nerve damage
- Lasting diplopia
- Allergic reaction to medications used
- Subarachnoid injection of local anesthetic
- Seizures
- Cardiorespiratory arrest
- Vascular complications, like compressive haematoma compromising retinal perfusion

Unfortunately, this has been hampering the drive for block specialization and training of ophthalmic anaesthesiologists, representing a failed opportunity for those patients who would benefit the most from their use. Nowadays, in fact, some authors are so keen on using topical anaesthesia that they even advocate its adoption in carefully selected patients proposed for vitrectomy<sup>5</sup> – something unthinkable until recently and with many detractors. This despite concerns regarding patient satisfaction and surgical conditions.

Boezaart et al. conducted an interesting study in which patients who had cataract surgery for both eyes in different moments in time were assigned to receive combined peribulbar-retrobulbar block on one eye and topical anaesthesia on the other. It was shown that patients generally preferred the intervention with the regional technique, which actually also helped make the surgery easier for the Ophthalmologist<sup>15, 16</sup>. Accordingly, regional techniques remain the preferred anaesthetic approach for cataract surgery in some countries<sup>17, 18</sup>, and are in fact regularly used at our own institution.

“Instituto Oftalmológico Dr. Gama Pinto” (IOGP) (Dr Gama Pinto Ophthalmology Center, located in Lisbon, Portugal) is a specialized stand-alone outpatient Ophthalmology centre whose Anaesthesiology team consists of 3 dedicated staff consultants performing peribulbar blocks on a routine basis since the year 2000, a fact that has allowed for considerable amount of experience to be gained. Considering the recent trend towards avoiding blocks in other countries, we decided to institute a register to keep track of all peribulbar blocks performed, so that an objective assessment of their safety could be made.

## II. METHODS

After obtaining approval from the local Ethics Committee we performed a retrospective analysis of the Anaesthetic register containing information from all patients who underwent a peribulbar block for ophthalmologic surgery at this Institution from December 1<sup>st</sup>, 2014 to September 1<sup>st</sup> 2015.

Throughout the study period no anaesthetic choices were influenced by the creation of the register, rather reflecting common local practice. Consequently,

whenever clinically indicated, in the absence of contraindications and after the patient had manifested his/her informed consent, patients presenting for different ophthalmic surgeries were submitted to peribulbar blocks for surgical anaesthesia.

The blocks were performed using a double-injection technique, with inferolateral and superomedial approaches. A 27 G, 25 mm long Ophthalmic cannula with bevel (Steriseal™, from Aspen Medical) was used, and a total volume of 1% ropivacaine cloridrate (Fresenius-Kabi™) ranging from 4,0 to 6,0 mL was administered, depending on the intended surgery and anaesthesiologist's preference. After injection, external compression was routinely applied with a Honan balloon inflated to a pressure of 30 mm Hg and kept on for 12 minutes. Following block installation, its success was classified semi quantitatively on a scale of 1 to 3, 1 being insufficient, 2 sufficient and 3 very good, both for the sensory and motor aspects of blockade.

All these data were inserted into the register and later used to build a database imported into IBM SPSS Statistics™ version 21, which was used for all statistical calculations. We supplemented this study with data from anonymous inquiries to the surgeons, so that their views on the blocks performed at the institution could be assessed.

## III. RESULTS

During the study period we performed 309 blocks in a total of 267 patients, which means that some patients (34) were operated on more than once in this timeframe with a peribulbar block. In fact, one patient was actually intervened 5 times, always with a peribulbar block (repeat vitrectomies, both eyes).

To facilitate a prompt understanding of the data obtained we present them graphically, with Tables 3 and 4 summarizing patient characteristics in the sample, Table 5 focusing on the surgeries performed and Table 6 on the peribulbar blocks themselves.



Table 3: Patient characteristics in the sample

Feature	Frequency	Percentage	
Age (years)	<40 years old	1	0,3%
	[40;50[ years old	4	1,3%
	[50;60[ years old	26	8,4%
	[60;70[ years old	71	23,0%
	[70;80[ years old	123	39,8%
	[80;90[ years old	77	24,9%
Sex	≥90 years old	7	2,3%
	Female	149	48,2%
	Male	160	51,8%
ASA Class	I	7	2,3%
	II	218	70,6%
	III	84	27,2%

Table 4: Frequency of different comorbidities in the sample

System	Disease	Frequency	Percentage
Cardiovascular system	Coronary artery disease	12	3,88%
	Previous myocardial infarction in the last 6 months	9	2,91%
	Aortic valve implantation	2	0,65%
	Heart failure	5	1,62%
	Arterial Hypertension	218	70,55%
	Atrial Fibrillation	15	4,85%
	Pacemaker	6	1,94%
	Other dysrhythmia	16	5,18%
Treatment with antiaggregant or anticoagulant drugs	Aspirin	62	20,06%
	Clopidogrel	15	4,85%
	Warfarin	9	2,91%
	Dabigatran	4	1,29%
	Rivaroxaban	2	0,65%
Endocrine system	Type 2 DM	85	27,51%
	Thyroid pathology	15	4,85%
	Obesity	10	3,24%
Psychiatric disturbances	Depression	16	5,18%
	Generalized anxiety disorder	20	6,47%
Neurologic system	Cerebrovascular accident / Transient ischaemic attack	18	5,83%
	Epilepsy	3	0,97%
	Dementia	2	0,65%
	Parkinson's disease	4	1,29%
	Hypoacusia	5	1,62%
Respiratory system	COPD	12	3,88%
	Emphysema	3	0,97%
	Asthma	5	1,62%
Miscellaneous	Rheumatoid arthritis	5	1,62%
	Chronic kidney disease	6	1,94%
	Hepatic dysfunction	3	0,97%
	Others	8	2,59%

**Table 5:** Characteristics of the surgeries performed under peribulbar block

Type of Surgery	Facoemulsification + intraocular lens implantation	147	47,6%
	Vitrectomy via pars plana / cerclage / endolaser	79	25,6%
	Vitrectomy via pars plana / cerclage / endolaser + IOL implantation	57	18,4%
	Trabeculectomy / ExPRESS™ valve placement / Cyclophoto-coagulation	26	8,4%
Duration of surgery	< 30 min	29	9,4%
	[30;60[ min	121	39,1%
	[60;120[ min	110	35,6%
	[120;180[ min	42	13,6%
	≥ 180 min	7	2,3%

As we can see most patients were elderly with comorbidities, the most common of which involved the cardiovascular system (in 75,7% of blocks). Of note, 77 patients were also on antiplatelet medications at the time of surgery, and 15 were previously anticoagulated, having stopped the appropriate medications according to their respective half-lives or, in the case of warfarin and acenocumarol, INR<sup>19</sup>.

Surgical procedures were divided into 4 classes for easier statistical treatment, with a clear predominance of facoemulsification and intraocular lens placement. Accordingly, almost half the interventions were relatively short (48,5% under 60 minutes). Sensory and motor block depth obtained is summarized in Table 6.

**Table 6:** Characteristics pertaining to the peribulbar blocks performed

Type of sedation for block	Propofol	134	43,4%
	No propofol (diazepam)	166	53,7%
	No sedation	9	2,9%
Volume of local anaesthetic administered	4,0 mL	16	5,2%
	4,5 mL	37	12,0%
	5,0 mL	124	40,1%
	5,5 mL	73	23,6%
	6,0 mL	59	19,1%
Degree of sensory block attained	1	6	1,9%
	2	49	15,9%
	3	254	82,2%
Degree of motor block attained	1	32	10,4%
	2	84	27,2%
	3	193	62,4%

**a) Complications**

There were no complications with lasting sequelae in any of the 309 blocks performed. However,

we did find a 2,9% rate of “adverse events”, in a total of 9 cases, described on Table 7.

**Table 7:** Adverse events related to block performance in our study

- 2 cases of activation of the oculocardiac reflex, which responded promptly to atropine administration (one had received 6,0mL of local anaesthetic, the other 5,5mL);
- 4 accidental vessel punctures (always in the inferolateral approach), solved with reorientation of the needle;
- 2 palpebral ecchymosis (minor, which reabsorbed in a few days);
- 1 patient proposed for vitrectomy who became markedly anxious despite previous explanation of the block procedure and mild pre-block sedation and ultimately had to be induced (conversion to general anaesthesia before the start of the surgery).

**b) Inferential analysis**

We analysed the relations between sensory block success and the different collected variables. The data obtained did not allow for valid use of Chi-square tests nor multinomial logistic regression due to a markedly dissimilar distribution between classes. Therefore, we decided to study the set of data by removing the 6 patients with failed (class 1) sensory block and used binary logistic regression to analyse the remainder (binary outcome: class 3 versus class 2 sensory block). With this strategy we obtained

statistically significant values for the relationship between the volume of local anaesthetic administered and the degree of sensory block obtained, with similar findings for the variables “type of surgery” and “use of propofol for sedation” (Table 8), but not for any of the comorbidities studied.

**Table 8:** P-value for different test statistics in univariate binary logistic regression models. The dependent variable is sensory block (grade 3 versus 2), with the independent variable being described in the left column

Independent variable	Omnibus test	Wald statistic	Hosmer-Lemeshow
Volume local anaesthetic	p<0,001	p<0,001	p>0,05
Type of surgery	p=0,003	p=0,005	p>0,05
Propofol use	p=0,001	p=0,002	p>0,05

We then built a multivariate logistic regression model, including the variables showing a positive relation to the outcome in the univariate analysis and assessing their significance when considered together. As shown in Table 9, all of them maintained statistical

significance. The resulting model was itself statistically significant, but there was still much variability not explained by it (Nagelkerke pseudo-R<sup>2</sup> of 0,234, correct classification rate of 84,8%, close to that of the null model).

**Table 9:** Characteristics of the multivariate binary logistic regression model built.

Model characteristics in general		
Omnibus test	p<0,001	Statistically significant (differs from the null model)
Hosmer-Lemeshow test	p=0,965	Adequate fit of the model to the data
Nagelkerke's pseudo-R <sup>2</sup>	0,234	Poor predictive value of the model
Correct classification rate	84,8%	Close to the null model's – poor discrimination of the model
Variable characteristics in the model		
Independent variable	Wald statistic	p-value
Volume local anaesthetic	19,961	P=0,001
Type of surgery	8,299	p>0,040
Propofol use	6,248	P=0,012

*c) Surgeon questionnaires*

Table 10 summarizes the results obtained from anonymous questionnaires answered by Ophthalmologists.

**IV. DISCUSSION**

Most patients in this study were elderly, with a mean age of 73,5 and a median of 74 years old – as was to be expected considering the surgeries performed. Also in line with what is described in the literature<sup>3</sup>, the most common comorbidities affected the cardiovascular, endocrine and neurologic systems, adding to the complexity of perioperative management and making the alternative of peribulbar blocks particularly appealing.

*a) Complications and adverse events*

We should emphasize the inexistence of major complications in either of the 309 blocks performed, which is significant. Most likely, as defended by other authors, the fact that there is a dedicated, experienced anaesthesiology staff<sup>3</sup> routinely performing these blocks had an important influence on this safety profile. Still, we should mention that serious complications of peribulbar blocks reported in the literature are in the range of 1:1000 blocks<sup>20</sup>, and that means our study is underpowered to draw strong conclusions as to their overall safety. The adverse events mentioned in Table 7 were all minor and easily solved.

We also find it important to emphasize that in 77 blocks (24,9%) the patients were taking antiplatelet

medications and in a further 15 (4,8%) they had been previously anticoagulated, having stopped the respective medications according to international guidelines<sup>19</sup>. These guidelines allow for block performance while on antiplatelet medications (as also defended elsewhere<sup>21-23</sup>), and also suggest appropriate courses of action for anticoagulation – which were followed. Neither anticoagulated nor antiaggregated patients had significant haemorrhagic complications, and even in the two cases where a minor palpebral ecchymosis developed post-block none of them were taking any of these medications. As for patients with accidental vascular puncture, one was concurrently medicated with aspirin but still did not develop ecchymosis nor signs of intraorbital haemorrhage. Despite the relatively small sample, these results support international findings concerning safety in this setting.

Some authors uphold that the greatest risk factor for haemorrhagic complications is vessel fragility (from diabetes, prolonged arterial hypertension) and not drug-induced dyscrasia<sup>19</sup>. The same authors also advocate that the use of small, short needles is instrumental in the prevention of haemorrhagic complications, and we followed that rule. As for the puncture technique, they do suggest the avoidance of the superonasal injection, which we actually employed routinely. Interestingly, in our series vessel puncture and ecchymosis formation only occurred as a result of the inferolateral injection – not the superomedial one.

Further studies with a larger sample size might help clarify the safety profile of this approach.

b) Effectiveness

Apart from safety, the second most important topic in peribulbar anaesthesia is no doubt its effectiveness rate, with some authors pointing the lack of predictability in block depth as its main drawback<sup>3</sup>. In some series the supplementation rate for peribulbar blocks is around 20%<sup>24</sup>, but can reach up to 66% when buckling surgery is considered<sup>25</sup>. In our study supplementation had to be performed in 6 cases (1,9%), but in an additional 15,9% the sensory block was not complete (grade 2), though deemed sufficient for surgery allowing adequate patient comfort and operating conditions with light<sup>26</sup> sedo-analgesia.

Regarding motor block, published studies attribute a 19%<sup>20</sup> to 28%<sup>24</sup> rate of poor akinesia to this type of anaesthetic technique. In our series, we had a total of 10,4% of blocks with insufficient (grade 1) motor block, and a further 27,2% of incomplete (grade 2) blocks, but such did not significantly impact the surgery.

c) Clues for improvement

Even though some authors found no correlation between volume of local anaesthetic and degree of block, they used volumes on average superior to ours<sup>27</sup>.

In our study, that relation was clearly present and statistically significant, not only as far as the amount of local anaesthetic is concerned but also in terms of type of surgery. While patients submitted to predictably more painful surgeries were already receiving a higher volume of local anaesthetic (at the anaesthesiologist's discretion), the lack of statistical significance for the interaction term between both in a logistic regression model evidences that this empirical compensation attempt did not completely succeed. The same is suggested by the fact that in more aggressive surgeries, even with larger volumes of LA, the percentage of complete sensory block was found to be smaller (Figures 1 and 2). Therefore, we should consider that patients submitted to vitrectomy (either alone or with facoemulsification and intraocular lens placement) may benefit from routinely receiving *higher volumes of local anaesthetic* than those actually administered in our daily practice. Further insight into the problem could be brought forth by the use of ultrasound to confirm adequate spread of local anesthetic<sup>13</sup>, the pattern of which appears to correlate with the efficacy of the block<sup>24</sup>. However, that is not routinely performed at our institution and corresponding data were thus not available in our series.

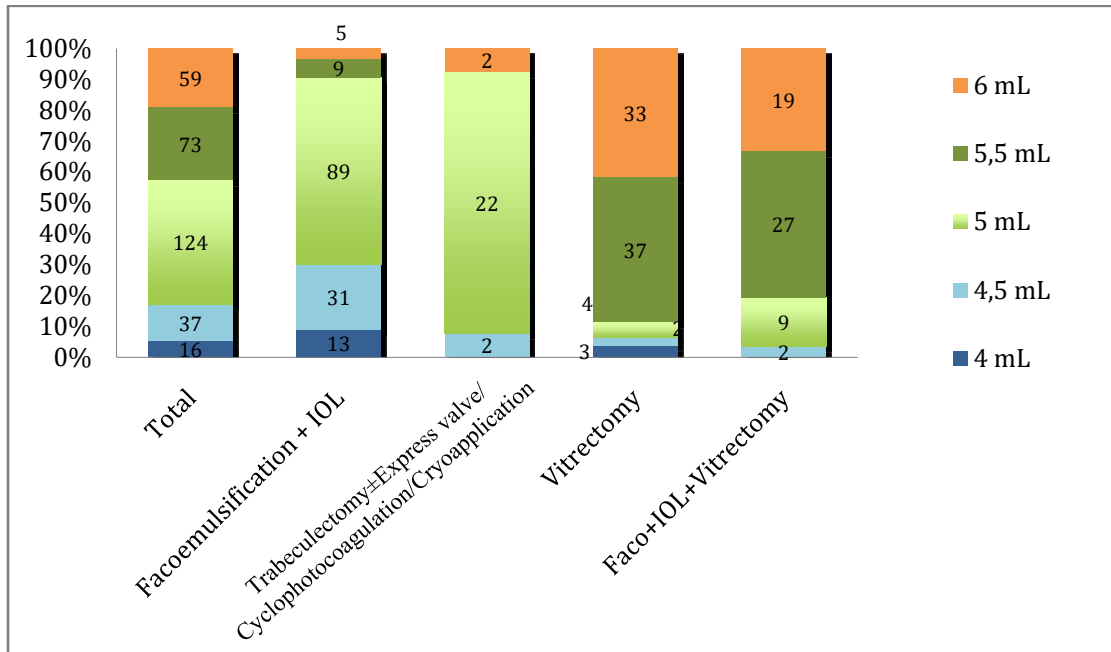


Figure 1: Volume of local anaesthetic (1% ropivacaine) administered per type of surgery

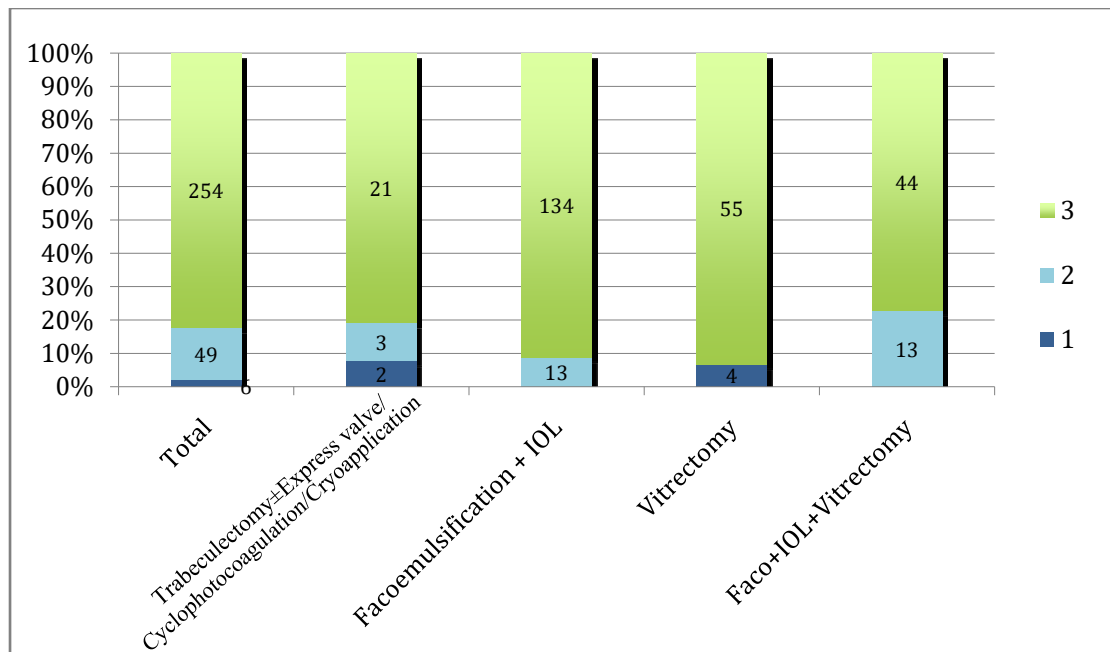


Figure 2: Sensory block obtained according to type of surgery

Another interesting point showing promise to improve our practice was the fact that *propofol administration* prior to the block procedure (on average 20mg) showed an OR of 2,462 (confidence interval: 1,215-4,991) in obtaining a class 3 as opposed to class 2 sensory block when compared to its absence (sedation with diazepam alone or no sedation). This suggests that patient conditions during block performance (anxiolysis, immobility and probably peribulbar muscle tone) are likely more favourable when propofol is used, suggesting we should rethink our practice in order to employ it more often. Clearly, future studies should assess whether such change could improve overall results. In the available literature some authors have suggested routinely including propofol in the sedation regimen for these patients, as a combination of midazolam, propofol and fentanyl in small doses<sup>28</sup> – though to our knowledge there was no proof of better block results consequent to its adoption.

d) *Thoughts on using the Honan balloon*

We have previously mentioned that at our institution ocular compression devices are routinely used after local anaesthetic injection, even though there is controversy in the literature concerning its efficacy. Some authors argue that compression has not been shown to enhance the quality of the block<sup>3</sup> and consequently elect not to use it routinely<sup>27</sup>. One study found no statistically significant changes in analgesia and/or akinesia with or without Honan balloon compression<sup>29, 30</sup>, but it should be emphasized that the minimum amount of local anaesthetic used was 7 mL – not 4 mL like in ours. Other authors<sup>8</sup> (though not all<sup>29</sup>) also mention that intraocular pressure (IOP) values before and after a period of balloon compression

following injection of small volumes of local anaesthetic are similar. Though this fact has not been specifically addressed in our work, we believe compression may be particularly important when small volumes of local anaesthetic are used, probably not so much from the point of view of lowering IOP after injection into a confined space (as the volume used was relatively small) but mainly to facilitate appropriate diffusion of the local anaesthetic. Still, our data cannot confirm or refute this reasoning, which is also doubtful in the literature. Should higher volumes of local anaesthetic start to be used routinely, as suggested by our data analysis, clearly this matter should be readdressed.

e) *Patient and surgeon satisfaction*

While we do not have objective data concerning patient satisfaction with peribulbar blocks, we asked ophthalmologists in anonymous questionnaires what was their take on the subject, given that they routinely follow patients early in the postoperative period. Analysing the data from the 25 inquiries returned to us we found that only one of those surgeons thought patients were dissatisfied with the technique, with 20 (80%) considering their patient’s satisfaction level was good or very good. The fact that 34 patients during the study period were operated on twice or more with peribulbar blocks also attests to their acceptance and satisfaction with the blocks, especially considering that their opinion is always taken into account at the time of choosing the anaesthetic technique.

One surgeon considered sensory-motor block to be usually inadequate with this technique, whereas the remaining 96% stated that it was usually adequate. 84% mentioned that their own degree of satisfaction with the technique was either good or very good, but none of



those inquired would elect a peribulbar block as a first choice for an uncomplicated facoemulsification procedure with intraocular lens implantation (Figure 3).

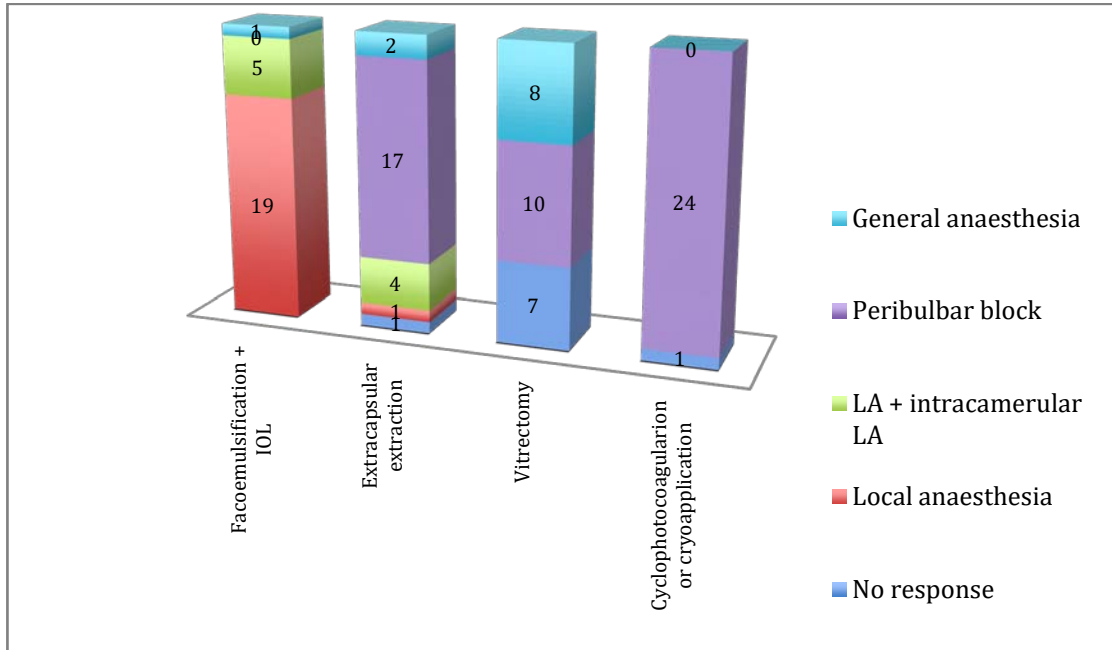


Figure 3: Surgeon's preference of anaesthetic technique for their patients for different types of ophthalmic surgery

It is interesting to note that if the surgeon's themselves were to be intervened on, a significant proportion would rather receive a general anaesthetic

(Figure 4), in frank opposition to what they chose for their patients.

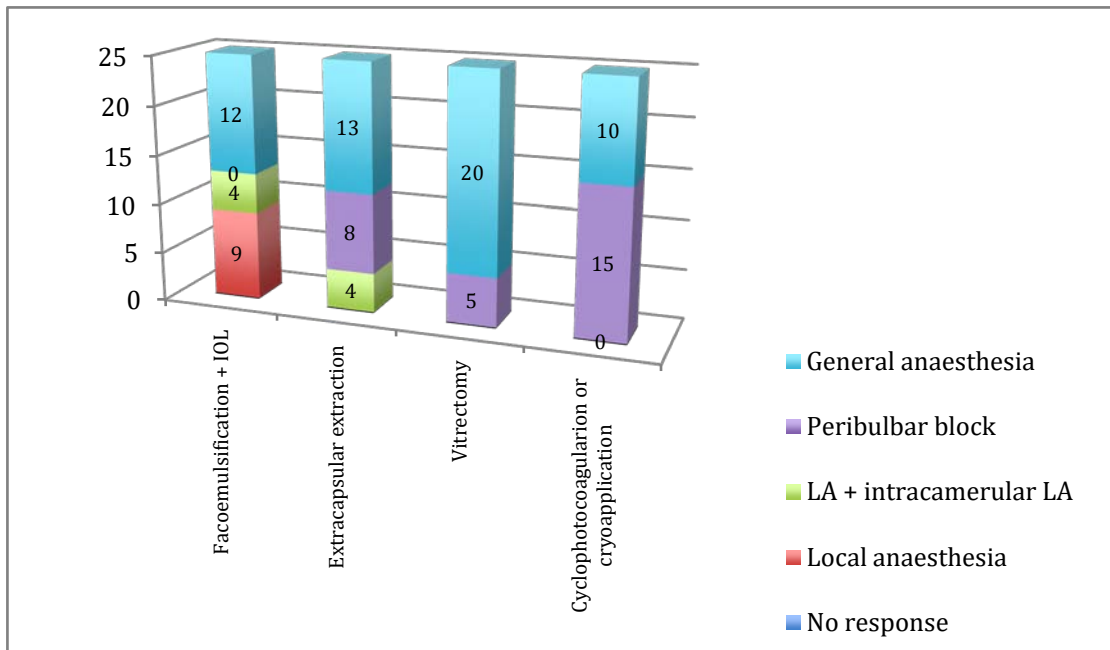


Figure 4: Surgeon's preference of anaesthetic technique for different types of ophthalmic surgery should they be the ones being operated on

f) Limitations to the study

Some limitations to the present study should be mentioned. To begin with, it was a retrospective study, drawing on previously collected data on the register,

and such clearly limits the analysis to existing information. As an example, the grading system used for assessment of block depth was qualitative, and it would be interesting to use existing validated scores such as



OASS (Ocular Anaesthetic Scoring System<sup>31</sup>). Given its retrospective nature, however, with pre-existing data coded differently, such was not possible.

It would also be interesting to analyse different aspects such as interference of block procedure on case turnover time, comparison of PONV and pain scores in patients submitted to peribulbar blocks versus general anaesthesia versus topical anaesthesia, but once again such data were not available for analysis.

Additionally, the fact that there was some variability in local anaesthetic volume administration, which was not protocolled but rather decided upon by the anaesthesiologist in normal daily practice taking into account the type of intended surgery, harboured a strong potential to become a confounding factor. However, statistical significance in the results obtained and testing for an interaction term minimized its influence.

Finally, we should realize that the rarity of complications advises larger studies to draw firm conclusions as to their incidence, and would also help create a logistic or even a multiple linear regression model with a higher discriminant value.

## V. CONCLUSION

Despite the existence of risks, the present work suggests a favourable safety profile for peribulbar blocks, even in antiaggregated/anticoagulated patients – at least when performed by experienced, dedicated anaesthesiologists. However, larger, adequately powered studies are advised to correctly define the incidence of complications.

Sample size limitations aside, some factors do appear to be positively related to the degree of intraoperative sensation, namely aggressiveness of surgery (naturally), amount of local anaesthetic administered and sedation with propofol versus diazepam for the block procedure. Because the latter two variables can easily be manipulated, they present an opportunity to improve local practice increasing block effectiveness rates and, ultimately, patient care.

### Competing Interests

The authors received no external funding for this work and have no competing interests to declare.

Table 10: Results from anonymous questionnaires to Ophthalmologists

Question	Possible options	Frequency	Percentage	
Professional experience	Resident	7	28%	
	Fellow for less than 5 years	0	0%	
	Fellow for 5-9 years	2	8%	
	Fellow for 10 or more years	16	64%	
If you could choose the anaesthetic technique for your patient, what would you prefer if he/she were to be submitted to:				
Facoemulsification + intraocular lens placement	Topical anaesthesia	19	76%	
	Topical anaesthesia + intracameral injection of LA	5	20%	
	Peribulbar block	0	0%	
	General anaesthesia	1	4%	
	No response	0	0%	
Extracapsular cataract extraction	Topical anaesthesia	1	4%	
	Topical anaesthesia + intracameral injection of LA	4	16%	
	Peribulbar block	17	68%	
	General anaesthesia	2	8%	
Vitrectomy	No response	1	4%	
	Peribulbar block	10	40%	
	General anaesthesia	8	32%	
Cyclophotocoagulation / cryoapplication	No response	7	28%	
	Topical anaesthesia	0	0%	
	Topical anaesthesia + intracameral injection of LA	0	0%	
	Peribulbar block	24	96%	
	General anaesthesia	0	0%	
No response	No response	0	0%	
	If you were to be operated on and could choose the anaesthetic technique for yourself, what would you prefer, according to proposed surgery:			
	Facoemulsification + intraocular lens placement	Topical anaesthesia	9	36%
		Topical anaesthesia + intracameral injection of LA	4	16%
		Peribulbar block	0	0%
General anaesthesia		12	48%	
No response		0	0%	
Extracapsular cataract extraction	Topical anaesthesia	0	0%	
	Topical anaesthesia +	4	16%	

	intracameral injection of LA		
	Peribulbar block	8	32%
	General anaesthesia	13	52%
	No response	0	0%
Vitrectomy	Peribulbar block	5	20%
	General anaesthesia	20	80%
	No response	0	0%
Cyclophotocoagulation / cryoapplication	Topical anaesthesia	0	%
	Topical anaesthesia + intracameral injection of LA	0	%
	Peribulbar block	15	60%
	General anaesthesia	10	40%
	No response	0	0%
Do you consider peribulbar blocks make surgery more difficult?	Yes	5	20%
	No	19	76%
	No response	1	4%
Do you think the degree of sensory-motor block obtained in most patients is adequate	Yes	24	96%
	No	1	4%
	No response	0	0%
On a scale of 1 (very bad) to 5 (very good), how would you rate your satisfaction with peribulbar blocks performed on your patients?	1 – Very bad	0	0%
	2 – Bad	0	0%
	3 – Satisfactory	3	12%
	4 – Good	17	68%
	5 – Very Good	4	16%
	No response	1	4%
On a scale of 1 (very bad) to 5 (very good), how would you rate your patients' satisfaction with peribulbar blocks?	1 – Very bad	0	0%
	2 – Bad	1	4%
	3 – Satisfactory	4	16%
	4 – Good	17	68%
	5 – Very Good	3	12%
	No response	0	0%
Have you ever had an important complication due to a peribulbar block	Yes	4	16%
	No	20	80%
	No response	1	4%
Do you consider peribulbar blocks safe?	Yes	22	88%
	No	3	12%
	No response	0	0%
Who do you think should perform peribulbar blocks?	Ophthalmologist	0	0%
	General anaesthesiologist	0	0%
	Anaesthesiologist dedicated to ophthalmic anaesthesia	25	100%
	No response	0	0%

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## Cornea in Wilson Disease: Kayser Fleischer Ring & Beyond

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**Abstract-** The identification of Kayser-Fleischer (KF) ring remains the most important clinical sign for the diagnosis of Wilson disease (WD). Slit lamp biomicroscope (SL) examination by a skilled observer is still the preferred method of evaluating KF ring. Anterior segment optical coherence tomography (AS-OCT) is an alternative method of evaluating KF ring in WD. Hyper-reflective layer in the corneal periphery at the level of Descemet membrane (DM) is the characteristic appearance of KF ring on AS-OCT. In a suspected case of WD, features of KF ring on AS-OCT may alert the clinician to do a careful SL examination to look for early KF ring. AS-OCT has been found useful in measuring the length of KF ring with ease even in patients with severe rigidity and children. AS-OCT can measure the length of KF ring better compared to SL in patients with limbal pathology. Early detection of increased corneal copper even before KF rings appear is a potential area for future research.

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# Cornea in Wilson Disease: Kayser Fleischer Ring & Beyond

Mittanamalli. S. Sridhar

**Abstract-** The identification of Kayser-Fleischer (KF) ring remains the most important clinical sign for the diagnosis of Wilson disease (WD). Slit lamp biomicroscope (SL) examination by a skilled observer is still the preferred method of evaluating KF ring. Anterior segment optical coherence tomography (AS-OCT) is an alternative method of evaluating KF ring in WD. Hyper-reflective layer in the corneal periphery at the level of Descemet membrane (DM) is the characteristic appearance of KF ring on AS-OCT. In a suspected case of WD, features of KF ring on AS-OCT may alert the clinician to do a careful SL examination to look for early KF ring. AS-OCT has been found useful in measuring the length of KF ring with ease even in patients with severe rigidity and children. AS-OCT can measure the length of KF ring better compared to SL in patients with limbal pathology. Early detection of increased corneal copper even before KF rings appear is a potential area for future research.

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## I. BACKGROUND

Dr. Samuel Alexander Kinnier Wilson described Kayser-Fleischer (KF) ring as a corneal ring of pigment of a greenish golden colour, associated with a form of cirrhosis of the liver, and also with nervous symptoms which belong to the lenticular group.<sup>1</sup> Till date, the description holds good and the identification of KF ring remains the most important clinical sign for the diagnosis of Wilson disease (WD). WD is an autosomal recessive disorder of copper transport, characterized by impaired excretion of copper into bile as well as incorporation into transporter copper protein ceruloplasmin.<sup>2</sup> Copper is an essential trace element. It is an important cofactor for many enzymes required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense and connective tissue formation.<sup>3</sup> The source of copper for the human body is the food consumed and the absorption depends on the copper content of food. The human gastrointestinal system can absorb 30 to 40% of ingested copper from typical western diets. Copper absorption occurs primarily in the small intestine and a small fraction from stomach.<sup>4</sup> Liver maintains adequate concentrations of copper in plasma. Clinical

manifestations are related to copper accumulation predominantly in the liver and brain.<sup>5</sup>

Though WD is thought to be an autosomal recessive disease, most affected individuals carry two different mutations (so-called compound heterozygotes) on each allele encoding the WD gene.<sup>6,7</sup> WD is due to mutations of the ATP7B gene on chromosome 13, which encodes a copper-transporting P-type ATPase (ATP7B) residing in the trans-Golgi network of the hepatocytes. ATP7B is responsible for transporting copper from intracellular chaperone proteins into the secretory pathway, both for excretion into bile and for incorporation into apo-ceruloplasmin for the synthesis of functional ceruloplasmin. The gene frequency in the healthy population is about one in 90. ATP7B is located on the long arm of chromosome 13 (13q14–q21). The most common mutation is the point mutation H1069Q in exon 14, accounting for 30–60% of all mutations in caucasian patients.<sup>2,6</sup> This mutation is associated with failure in catalytic phosphorylation and mislocalization of ATP7B. Mutational analysis has helped us to understand that the prevalence of WD being higher than traditionally perceived.<sup>8</sup>

## II. DIAGNOSIS OF WD

The worldwide prevalence of WD is estimated to be between 1 in 30,000 and 1 in 100,000 with a gene frequency of 0.56% and a carrier frequency of approximately 1 in 90.<sup>2</sup> It is even higher in certain populations with consanguinity.<sup>2</sup> WD should be considered in any person between the age of 3 and 55 years with typical symptoms and signs.<sup>9</sup> The most common presentations are with liver disease or neuropsychiatric disturbances. Asymptomatic patients are most often detected by family screening.<sup>5</sup> Late onset of symptomatic WD disease may occur occasionally. Neurologic signs are variable, most often tremor, ataxia, and dystonia. The most common form of tremor in WD is an irregular, and somewhat jerky, dystonic tremor.<sup>10</sup> Asymptomatic hepatomegaly, isolated splenomegaly, persistent elevations in serum aminotransaminases, jaundice, fatty liver, resembling autoimmune hepatitis, acute hepatitis, compensated or decompensated cirrhosis and acute liver failure are reported liver manifestations in WD.<sup>9</sup> Psychiatric manifestations include depression, neuroses, personality changes and psychosis.<sup>11</sup> Renal abnormalities which are rare include aminoaciduria and nephrolithiasis.

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Presence of KF rings and serum ceruloplasmin concentrations of less than 20 mg/dL are sufficient to establish the diagnosis.<sup>12</sup> The first step in screening for potential WD is often serum ceruloplasmin measurement.<sup>13</sup> When KF ring is not present (as is common in the hepatic manifestation of WD), ceruloplasmin levels are not always reliable. Serum ceruloplasmin may be decreased (autoimmune hepatitis, severe hepatic insufficiency in advanced liver disease, celiac disease, familial aceruloplasminemia, or in heterozygous carriers of ATP7B mutations) or increased (inflammation in the liver or elsewhere) in diseases other than WD.<sup>5</sup>

The routine tests which are done in the diagnosis of WD include serum ceruloplasmin (decreased by 50% of lower normal value), 24-hour urinary copper  $>1.6 \mu\text{mol}/24 \text{ h}$  in adults and  $>0.64 \mu\text{mol}/24 \text{ h}$  in children, serum "free" copper  $>1.6 \mu\text{mol}/\text{L}$ , hepatic copper  $>4 \mu\text{mol}/\text{g}$  dry weight and identification of KF rings by SL examination.<sup>5</sup> Urine copper excretion measurement after a penicillamine challenge is considered a diagnostic tool for WD, and it has been commonly considered diagnostic when  $>1600 \mu\text{g}/24 \text{ h}$ . This test is not recommended in children without symptomatic liver disease, because only patients with severe liver damage due to WD are likely to have a positive test.<sup>14</sup> In absence of KF ring, WD is difficult to diagnose and even centers with expertise regard diagnosis as a challenge in some cases.<sup>15</sup>

### III. KF RING IN WD

KF ring is corneal copper deposition in the inner parts of Descemet membrane (DM) in the form of granules.<sup>16</sup> Histochemistry, electron microscopy and electron probe x-ray microanalysis have reported copper deposits within the periphery of DM causing KF ring.<sup>17-20</sup> Electron microscopy studies have identified copper bound to sulphur-containing moiety in electron dense granules seen throughout the cornea in patients with WD. It is 10 to 20 times higher in the corneal periphery. These granules are arranged in multiple, discrete layers with the smallest granules closest to the endothelium.<sup>19</sup>

Almost all patients with neuropsychiatric symptoms will show KF rings, whereas about 50–60% of patients with hepatic WD will have this manifestation.<sup>7</sup> Cases of neurologic WD with no KF ring is regarded as less invasive form of WD.<sup>21</sup> It is seen in nearly 40% of pre-symptomatic WD patients.<sup>22</sup> The KF ring increases as the disease progresses. The morphological findings of copper deposits seem to differ from patient to patient depending on the stage of the disease. The ring is typically seen in the peripheral cornea, copper deposited on DM as greenish yellow or golden brown ring. (Figure1). The color of the KF ring and its localization seems to be related to the peculiar

multilaminar arrangement of granules in the periphery.<sup>19</sup> It is almost always bilateral, starts superiorly first, then inferiorly and later becomes circumferential.<sup>16</sup> Though it is reported that in children presenting with liver disease, KF rings are usually absent, in our series of 10 patients, two were less than 12 years of age. Both had liver manifestations. There are case reports where KF ring was the first detectable manifestation of WD.<sup>23</sup> Significant correlations between KF at diagnosis and clinical neurological manifestations has been reported.<sup>24</sup> KF ring appears to be a predictive factor in the neurological and hepatic evolution of WD.<sup>24</sup>

### IV. MECHANISM OF FORMATION OF KF RING

The source of copper for incorporation into DM is not very clear. It is postulated that ionic copper loosely bound to albumin has its origin in the anterior chamber. Elevated levels of copper in the aqueous humor in patients with WD have been reported.<sup>19</sup> K-F ring is believed to be formed by the copper particles which infiltrate into DM through the endothelial cells from the aqueous humor. Finding of intracytoplasmic copper granules in endothelium, suggests a role for endothelium in absorption of copper from aqueous humor.<sup>25</sup> Tso et al proposed that cellular activity is required for deposition of copper material into the thick basement membrane.<sup>26</sup> The pattern of dense copper deposition in the periphery is attributed direction of aqueous flow and / or functional peculiarity of the peripheral corneal endothelium. The microenvironment of anterior chamber may be the key factor that affects the transfer of copper to basement membrane.<sup>25</sup> Other than aqueous humour, the other possible source of copper is limbal circulation. Innes et al reported a case of unilateral KF ring.<sup>16</sup> The eye without the ring was injured in childhood and had a low intraocular pressure. They postulated that the copper deposition is through aqueous (which was reduced in the eye with low intraocular pressure), rather than limbal circulation which was normal in the scared eye. The limbal circulation of the patient's right eye was not disturbed though it had a corneal scar and the intraocular pressure was low.

Cornea is also permeated by ionic copper. This accounts for high concentration of the copper in the cornea and lack of correlation between KF ring and corneal copper. Electron microscopy of KF ring showed the presence of electron dense deposits of varying size mainly in the DM.<sup>27</sup> They are arranged essentially in the middle third and in two linear zones. Posteriorly in relation to the endothelial surface, the deposits were fine and dust-like. Anteriorly towards the stromal surface they were fewer number but larger in size. The larger deposits with a central nidus probably result from coalescence of the smaller particles over a period of time. It is not clear why the deposits are at the periphery. It may be related to the direction of aqueous flow or to

some functional peculiarity of the peripheral corneal endothelium.

## V. METHODS OF EVALUATING KF RING

1. Naked eye examination of KF ring is less sensitive method compared to SL. On naked eye examination, thick KF rings are visible as yellow or brown rings in the peripheral cornea.
2. Direct ophthalmoscope can be used as a bed side evaluation method of thick KF rings. Early KF rings can be missed.
3. Slit lamp biomicroscope (SL) using a gonioscope- This method used to assess the angle of the eye. Early KF ring is visible as deposit in Schwalbe's line of angle, which is where the DM of cornea terminates. Performing and interpreting gonioscopy required expertise.
4. Slit lamp biomicroscope (SL) using diffuse and direct focal illumination- A SL by an experienced/ skilled observer is required to identify KF rings.<sup>5</sup> SL was invented by Gullstrand in 1911.<sup>28</sup> On SL, using diffuse illumination and direct focal examination, KF ring is seen as seen as golden-brown, brown-green, green-yellow, golden-yellow, bronze or reddish-brown coloring of the DM in the peripheral limbal area of the cornea. (Figure Rarely the color of the deposit may be ruby red, bright green or ultramarine blue in color.<sup>19, 29</sup>

In long standing cases, the deposits become thick and granular. The larger KF ring size correlates to WD severity.<sup>30</sup> The deposits rarely are seen more than 5mm centrally and gradually fade towards the centre of the cornea. The description of a clear ring of peripheral cornea to the K-F ring seems to be because of variable position of Schwalbe's line. The intensity of KF ring seems to be correlated to the severity of WD. KF ring does appear to be a predictive factor in the neurological and hepatic evolution of WD.<sup>24</sup>

5. Scheimpflug photography & Imaging The usefulness of Scheimpflug photography in the follow-up of WD disease patients has been presented in one case by Obara H1 et al.<sup>31</sup> In the case presented by them, during 15 year follow-up the yellowish-brown granular opacification on the anterior lens capsule had mostly disappeared, but the same type of opacification had emerged on the posterior lens capsule, showing disease progression. The changes in the lens were difficult to detect by SL examination alone, but were clearly picked up by Scheimpflug slit images. The authors suggested this modality is valuable in follow-up studies of eye involvement in WD.

Telinius N et al suggested Schiempflug imaging as an important tool to diagnose KF ring.<sup>32</sup> On Scheimpflug images, the KFR could be seen as a

- bright subendothelial band peripherals. Patients with a KF ring, had a significantly higher subendothelial signal compared to both WD patients with a KF ring and the control group.
6. In vivo confocal microscopy – Ceresara G et al reported the confocal microscopy of corneal copper in a series of 20 WD patients.<sup>33</sup> Laser scanning confocal microscopy showed peripheral hyper reflective granular micro deposits at the level of Descemet's membrane in 75% of patients whereas peripheral corneal deposits were found in 25% patients by means of traditional slitlamp and goldman three mirror lens. Confocal grading of the superior cornea was significantly higher than in other quadrants.
7. Anterior segment optical coherence tomography (AS-OCT)

### a) AS-OCT findings of KF ring

In the last two years, I have evaluated 10 patients with KF ring seen on SL, by AS-OCT. First introduced by Izatt et al. in 1994, AS-OCT is a noncontact and non-invasive imaging technique that captures high resolution cross-sectional images of the anterior segment.<sup>34</sup> AS-OCT has been found to be useful in exploring the anterior segment of the eye, mainly the cornea, anterior chamber and chamber angle.<sup>35</sup> OCT imaging is based on measuring the delay of light (typically infrared) reflected from tissue structures. The technology utilizes a Michelson interferometer, which creates a reference beam usually of infra-red light against which it measures multiple other beams of light as they return from the variably reflective tissue layers of the eye. The device collects reflected light from the sample at reference beams, thereby creating an interference pattern. My experience of AS-OCT of KF ring in a retrospective case series of 7 WD patients was presented.<sup>36</sup> The KF ring on grey scale of AS-OCT was visualized as hyper-reflective deep corneal layer at the level of DM in all eyes. The OCT color scale revealed KF ring as a greenish/greenish yellow/yellow/ yellow orange band. The grey scale of AS-OCT was found to measure with relative ease the length of KF ring in two patients. I suggested that AS-OCT is an alternative method of evaluating KF ring in WD which can be used in combination with SL examination and KF ring can be easily measured using the grey scale of AS-OCT.

### b) Advantages of evaluating KF ring by AS-OCT

AS-OCT as an alternative method of looking at KF ring. Detection of KF ring on SL requires experience of a clinician. An ophthalmologist, who has not seen KF ring on SL before, may miss an early KF ring. On the other hand in a suspected case, hyper-reflectivity of deep corneal layer in the periphery on AS-OCT may alert the clinician to do a careful SL examination to look for early KF ring. Non – Ophthalmologists like neurophysicians and gastroenterologists may be able to

look at KF ring on AS-OCT.<sup>37</sup> AS-OCT was found useful in measuring the length of KF ring. Method of measuring KF ring and calculating KF ring score has been suggested by Esmaeli et al.<sup>38</sup> Standard narrow-beam direct illumination slit-lamp photographs (20 x magnification) were taken at 6 o'clock and 12'o clock vertical corneal meridians in each eye. After masking and randomizing the photographic slides, a single observer measured the length of KF ring at 6 o' clock and 12'o clock vertical corneal meridians using a Castroviejo caliper under 4 x magnification. The average KF ring score was obtained by summation of all vertical length measurements in both eyes as per the number of meridians examined by SL photomicrographs. The nasal and temporal rings were not measured due to technical difficulty using slit-lamp photographs in these meridians. With eye aligned properly and cursor positioned, KF ring can be easily measured using the grey scale of AS-OCT. Even nasal and temporal measurements could be obtained and when the measurement is less than 1 mm, the KF ring measurement in microns is given on grey scale. Using AS-OCT, KF ring can be easily measured in patients what are not co-operative for SL examination. With a combination of KF ring & signal density, KF ring can be quantified using AS-OCT.<sup>39, 40</sup> WD patients with severe rigidity who cannot be examined by SL can have AS-OCT evaluation and length of KF ring measured. AS-OCT can be performed in children and even in neonates. AS-OCT evaluation of congenital corneal opacities between 2 days and 2.5 years of age has been reported.<sup>41</sup> Recently, I saw a 12 year old male with liver failure and cirrhosis who was diagnosed as WD based on presence of KF ring and low serum ceruloplasmin. In this case, the hyper reflective pattern in the peripheral DM membrane was seen despite increased limbal pigmentation. The length of KF ring measured using SL was less compared to AS-OCT because of increased limbal pigmentation as limits of KF ring could not be clearly delineated as pigmentation was extending into cornea (Figure2). Hyper reflectivity on grey scale and its measurement is shown in Figure 3. This case suggests that AS-OCT can measure the length of KF ring better in patients with limbal pathology.

c) *Possible other advantages of using AS-OCT in evaluating KF ring which needs to be studied further*

AS-OCT can possibly determine the density of KF ring and hence help us to assess the severity of disease. Anti-copper therapy leads to KF regression. No significant correlations were observed between KF regression and clinical neurological or neuro-imaging improvement nor between KF modifications and clinical hepatic improvement.<sup>24</sup> The reappearance of KF ring in a medically treated patient suggests non-compliance with therapy. AS-OCT can be a good tool to assess response and compliance to treatment in WD. Further

studies are required to confirm the advantages stated above.

Case reports of pigmented corneal rings similar to KF ring have been reported in patients with chronic aggressive hepatitis, cryptogenic cirrhosis and alcoholic patient with cirrhosis with normal serum and liver copper levels.<sup>42-47</sup> We need to study all patients with liver cirrhosis for corneal deposits with SL, AS-OCT and also perform genetic analysis. These patients may be heterozygous carriers of ATP-7B mutations with associated liver disease who do not show copper overload disease and inflammation of liver or elsewhere could have caused the ceruloplasmin concentration to rise to normal level or be high, as it is an acute phase protein.

AS-OCT can differentiate KF ring of WD from hypercupremia of other causes and further studies are required in this direction. In WD, the hyper-reflectivity is in the peripheral cornea at the level of DM, whereas in hypercupremia of other causes, the hyper-reflectivity can be expected to be seen in the para-central or peripheral cornea at the level of DM.

## VI. DIFFERENTIAL DIAGNOSIS OF KF RING

Though KF ring is said to be diagnostic of WD, corneal pigment rings have been reported in various other liver diseases and hypercupremia of various causes. Corneal pigment rings should not be regarded as pathognomonic of WD in the absence of neurological symptoms.<sup>16</sup> It is recognized that KF like rings occur in other conditions, particularly when severe cholestasis is a feature. Pigmented corneal rings similar to KF ring have been reported in patients with primary biliary cirrhosis and progressive intrahepatic cholestasis of infancy and childhood.<sup>19,39,44,45</sup> In patients with primary biliary cirrhosis, these rings were described as yellowish-green or golden- brown in color and extended around the periphery of each cornea in the region of DM. The rings were seen only by SL and not with unaided eye or an ophthalmoscope. These rings resembled KF rings seen in early or minimal manifestations of WD. They are not reported to be thick and granular. All these patients were associated with high levels of hepatic copper, serum copper, urinary copper and serum ceruloplasmin. Pigmented corneal rings in this situation is believed to be because of long standing cholestasis in which an excessive copper deposition occurs in the liver and in other organs due to failure of biliary copper excretion.

Case reports of pigmented corneal rings similar to KF ring have been reported in patients with chronic aggressive hepatitis, cryptogenic cirrhosis, and alcoholic patients with cirrhosis with normal serum and liver copper levels.<sup>42-49</sup> In chronic active hepatitis, it was seen as crescents superiorly and inferiorly of a yellow-green colour.<sup>42</sup> They have also been described as



brownish pigmentation around the entire periphery of each cornea or as bilateral circumferential KF rings. The deposits in this situation have been called as pseudo-KF rings or KF-like rings. These patients had normal or high serum ceruloplasmin levels. The nature of these deposits is not clear as in one patient, the intensity of his rings was noted to fluctuate with his serum bilirubin concentration. It was speculated that bilirubin could produce at least some of the pigment in patients with KF-like rings. Phinney RB et al four patients with corneal staining who had total bilirubin levels more than 26 mg/dl. Bilirubin pigmentation was more prominent in the peripheral than central cornea. In one patient of this series evaluated by SL, the epithelium was intact and entire stroma was stained yellow, more densely in the peripheral 2 to 3 mm.<sup>50</sup>

The deposition of copper on DM has also been reported in cases of hypercupremia associated with multiple myeloma, pulmonary carcinoma, benign monoclonal gammopathies, chronic lymphocytic leukemia and secondary to oral contraceptives.<sup>51-56</sup> They have also been reported with schistosoma infection, galactosialidosis, and intraocular copper foreign body.<sup>57</sup> These patients were found to have abnormally elevated serum copper and elevated or normal ceruloplasmin levels. Copper deposition in malignancies and secondary to oral contraceptive use was seen as bluish-green or greenish brown in color and it involved the paracentral or central cornea.

## VII. KF RING FOLLOWING TREATMENT OF WD

K-F rings are reversible with medical therapy or after liver transplantation.<sup>58-60</sup> The reappearance of either of these eye changes in a medically treated patient suggests non-compliance with therapy. Esmali et al found the average rate of reduction in KF ring size was 14% per year.<sup>36</sup> The KF rings disappear on treatment first in the nasal and temporal aspects, before the inferior and superior cornea.<sup>29,38</sup> There appears to be a correlation between KF ring regression and improvement in brain MRI.<sup>24</sup> There is lack of correlation between KF rings and neurologic findings and despite complete disappearance of KF ring, patient may be neurologically disabled.<sup>59</sup>

## VIII. ASSESSING COPPER CONTENT OF CORNEA

KF ring does not represent the total copper content of cornea. Belkin M et al measured corneal content by X-ray excitation spectrometry in two controls and in seven patients of WD.<sup>61</sup> Two patients were on D-Penicillamine for three to four years, had no detectable KF ring, were in excellent clinical condition and their copper signals were normal. One patient had an indistinct KF ring and a much higher copper signal. One patient had a prominent ring, but a low copper signal.

Patient 5, was allergic to D-penicillamine, was examined before and after a course of dimercaprol. The copper signal fell to 45% after dimercaprol, although the appearance of her KF ring did not change. Patient 6 was in poor clinical condition, had a very indistinct KF ring, but had a high copper signal. Patient 7 was diagnosed 13 years ago. She had received D-penicillamine for the first 2 years only and was on no treatment since then. Her KF ring was seen with naked eye, and the corneal copper concentration was at least 10 times higher than those other patients. Based on the results it was inferred that KF ring is a crude indicator of corneal copper content, and appearances were not correlated with the measured corneal signal. The authors highlighted that they could detect changes in corneal copper content which SL examination missed.

Though identification of KF rings by ophthalmologists helps in diagnosis of WD, it is important to realize that by the time KF ring appears, significant other potential life threatening tissue damage involving the liver and central nervous system would have already appeared. Challenge in WD would be to detect increased corneal copper before KF ring appears. In vivo detected of increased copper in cornea would be useful for early diagnosis, assess treatment response and also to find the compliance to medical treatment in WD. Research in this direction needs to be re-initiated. X-ray fluorescence (XRF) spectroscopy which is found suitable for investigating the elemental composition of biological tissues, has been recently used to find copper in liver specimens.<sup>62</sup>

## IX. CONCLUSIONS

SL examination by a skilled observer is still the standard method of evaluating KF ring In WD, AS-OCT is an alternative method of evaluating KF ring in WD. Further studies are required to study the potential advantages of AS-OCT including assessing the density of KF ring, as a tool to assess response to treatment in WD, in differentiating KF ring of WD disease from copper deposits in hypercupremia and pigmented corneal rings in non-Wilsonian liver disease. In-vivo methods need to be developed to determine corneal copper content

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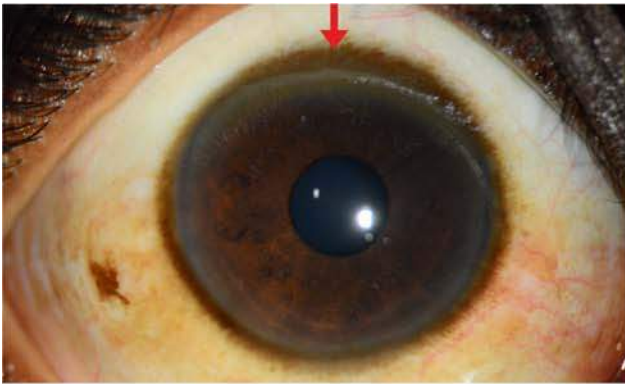
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FIGURE CAPTIONS



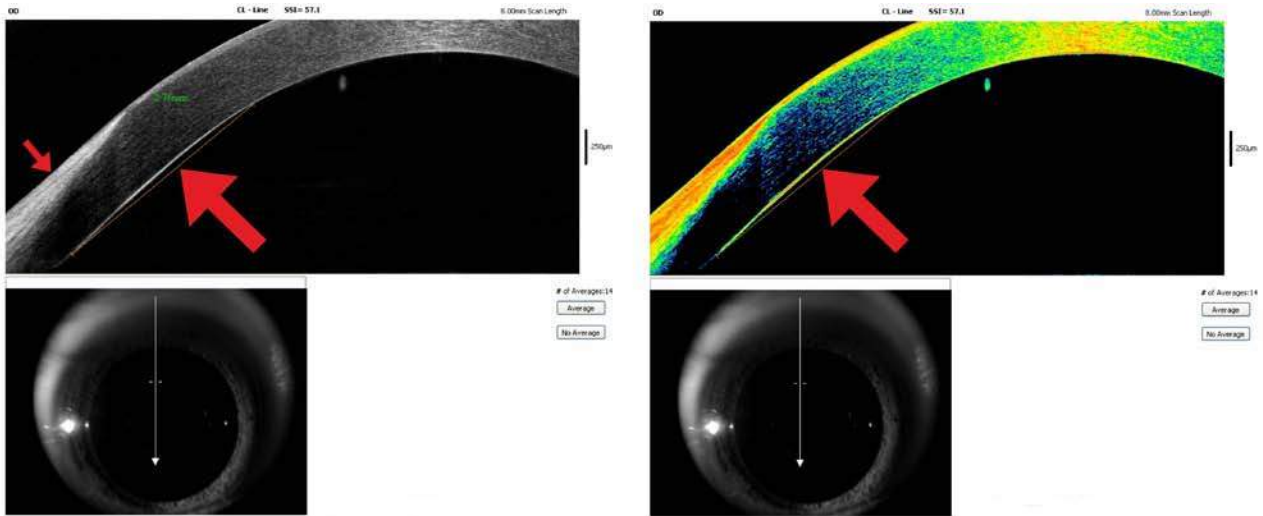
*Figure 1:* Thick yellowish brown deposit in the superior corneal periphery (arrow), Kayser-Fleischer ring which is peripheral corneal cuprosis



*Figure 2A:* Slit lamp –diffuse view of right showing limbal pigmentation (arrow) and Kayser-Fleischer ring



*Figure 2B:* Slit lamp - slit view of right showing brownish green deposit in the corneal periphery (arrow)



*Figure 3A:* Anterior segment optical coherence tomography grey scale analysis of right eye showing hyper reflectivity (large arrow) at the level of Descemet's membrane. Note the hyper-reflectivity (small arrow) because of increased pigmentation from limbal epithelium

*Figure 3B:* Colour scale of anterior segment optical coherence tomography of right eye showing orange yellow band (arrow) at the level of Descemet's membrane

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## Characteristics and Outcomes of Patients with Primary Central Nervous System Lymphoma

By Hatice Terzi, Çağrı Canbolat, Hüseyin Bozkurt, Serdal Korkmaz, Ünal Özüm,  
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**Abstract- Background:** The aim of the present retrospective study was to review the clinicopathological characteristics and outcomes of primary central nervous system lymphoma (PCNSL) cases at our institute.

**Methods:** Patients diagnosed with PCNSL at our institute from August 2010 to May 2015 were evaluated. During the said period, a total of 14 cases were diagnosed with PCNSL.

**Results:** Deep frontal lobe was the most common site of involvement while diffuse large B-cell lymphoma (DLBCL) was the most common histological pattern. 10 patients were treated with 3.0 g/m<sup>2</sup> methotrexate (MTX) intravenously concomitant with intraventricular 15 mg MTX and 2 patients were treated with radiotherapy (RT). Two of the patients died due to respiratory failure a short time after the treatment started. The median overall survival (OS) was 8 months (minimum: 1 months, maximum: 15 months) and the median OS was 12.42±13.20 months (min: 1 month, max: 48 months).

**Keywords:** methotrexate, overall survival, primary central nervous system lymphoma, radiotherapy.

**GJMR-F Classification:** NLMC Code: WH 525



*Strictly as per the compliance and regulations of:*



# Characteristics and Outcomes of Patients with Primary Central Nervous System Lymphoma

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**Conclusion:** As stated in the previous studies, MTX-based chemotherapy regimens are still the most effective treatment option in this patient population.

**Keywords:** methotrexate, overall survival, primary central nervous system lymphoma, radiotherapy.

## I. INTRODUCTION

Primary central nervous system lymphoma is a rare type of cancer accounting for less than 3% of all the brain tumors. Majority of the primary central nervous system lymphoma are diffuse giant B cell lymphoma.

The yearly incidence of PCNSL is 0,5 cases per 100 000 people. The incidence is higher in immunocompetent individuals, whereas it seems to be lower in patients with HIV infection. Median age at diagnosis is 60–65 years<sup>2,3</sup> and median survival is 10–20 months, with a survival rate of less than 20–30% at 5 years.<sup>4,5,6,7,8,9</sup>

Unlike in systemic lymphomas, long term remission is very in PCNSL. Chemotherapy, radiotherapy, surgery and a combination of these can be used in intracranial lymphomas.<sup>10</sup>

While combined chemotherapy and RT produces response rates of up to 80–90% and median

OS close to 5 years in PCNSL<sup>11,12,13</sup> neurocognitive toxicity stands as the major limitation of the said combined treatment.<sup>14</sup> Delayed neurotoxicity presenting itself with memory deterioration and personality changes early in the course is followed by gait disturbance and urinary incontinence, all of which are generally permanent.<sup>14</sup>

The prognosis and outcome of treatment differ in younger and older patients. Interestingly, when compared those who did not receive radiation, the outcomes are not improved when radiation is added to the treatment regimen of elderly patients. The optimal combination regimen or dose of MTX remains to be elucidated.

Currently, the treatment for PCNSL often involves high-dose MTX (HD-MTX) based chemotherapy with or without whole brain radiotherapy (WBRT). While both MTX and WBRT may cause CNS damage, there is a synergistic toxicity when these two modalities are combined.<sup>15,16</sup> The present retrospective study reviews our experience on patients with diagnosed PCNS at our single centre.

## II. PATIENTS AND METHODS

The study was conducted on patients histologically diagnosed with PCNSL at our institute from August 2010 to May 2016. The neurological tumour tissue for diagnosis was obtained by stereotactic or craniotomy. The Haematoxylin and eosin (H&E) stained slides were reviewed and the complete clinical details were obtained from patient records. Age, sex, radiological findings, immune status, and human immunodeficiency virus (HIV) serology findings were recorded in each case. The possibility of secondary involvement by a systemic lymphoma was excluded by obtaining the details pertaining to lymphadenopathy, organomegaly, and bone marrow study. Cerebrospinal fluid (CSF) findings were recorded whenever available.

### a) Patients

Fourteen patients were diagnosed as PCNSL with histological confirmation. Clinical data for all patients constituting the study cohort were available. All patients had one or more intracranial mass lesions. Histological confirmation of PCNSL was made through brain biopsy or open biopsy. Systemic lymphoma was excluded through staging evaluation by neck, chest,

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abdominal, and pelvic computed tomography (CT) and by bone marrow biopsy. Thirteen patients underwent cranial neuroimaging at diagnosis by magnetic resonance imaging (MRI). Only one underwent contrast-enhanced cranial CT due to having hip prosthesis. Fourteen patients underwent lumbar puncture and a complete ophthalmologic evaluation including a slit-lamp examination. Testicular ultrasonography was performed in male patients. There were no laboratory abnormalities before chemotherapy and the laboratory diagnosis of a latent or obvious infection was excluded.

#### b) Immunohistochemistry

Histological subtype of the tumour with grading of tumour cells on haematoxylin and eosin-stained slides, along with immunohistochemical details, including typing for leucocyte common antigen (LCA), CD20 (B cell marker) and CD3 (T cell marker), performed on formalin-fixed, paraffin-embedded tissue samples, were recorded.

#### c) Treatment protocol

In DLBCL patients, treatment consisted of six cycles of chemotherapy administered at 28-day intervals, consisting of the following: MTX 3.0 g/m<sup>2</sup> for one day, followed by 15 doses of leucovorin rescue. At diagnosis, 8 patients underwent to Ommaya reservoir implantation and 6 courses of intraventricular MTX (15 mg) at 3-day cycle were administered to the patients. RT has been given in 2 patient. One of these patients had low grade lymphoma and the other had diffuse giant cell lymphoma. DLBCL patients were treated with a chemotherapy.

#### d) Follow-up

Repeat neuroimaging was conducted by MRI or CT at the completion of 3 chemotherapy cycles and then the completion of 6 chemotherapy cycles and lastly every 3 months. 1.5T clinical scanner was used during MRIs. The deep brain structures defined were basal ganglia, the corpus callosum, brain stem and cerebellum. Peritumoral edema was categorized as < or ≥ 2 cm from the brain tumour as assessed in T2-weighted MR images.

#### e) Evaluation of response to treatment

The standardized criteria of the National Cancer Institution on the changes in the size of enhanced lesions on T1 weighted MR images were used to define the treatment response. Complete remission (CR) was defined as the complete disappearance of lymphoma while partial response (PR) as ≥ 50% decrease in tumour size, progressive disease (PD) as a ≥ 25% increase in tumour size or the appearance of any new lesion and stable disease (SD) as situations that did not meet any of these three previous criteria.

The International Extranodal Lymphoma Study Group (IELSG) score was used to define the risk group. Using the prognostic scoring system of the IELSG, the

patients were categorized into three risk groups as low, intermediate, and high. Age, ECOG performance status grade, lactate dehydrogenase (LDH) serum level, protein concentration in CSF, and involvement of deep brain structures were the variables included.

#### f) Statistical methods

OS was calculated from the date of histological diagnosis to death or the last date of follow-up. Both median OS and mean OS was determined.

#### g) Ethics statement

The approval for this study was obtained from the Ethical Committee of Cumhuriyet University Clinic Researches.

### III. RESULTS

#### a) Patients and treatment

The study group consisted of 14 patients, including 5 females and 9 males. At least one of the prognostic factors was poor in all patients. The median age of the patients was 62 years (range; 42-80). 12 patients had single lesion while the most common site of involvement was the deep frontal region.

In 2 patients, MRI showed multiple site of involvement. Cerebellar involvement was very rare (1 patient) (Figure 1). While 13 of the patients were diagnosed with DLBCL, one of the patients was diagnosed with low grade lymphoma.

The obtained samples did not reveal any CFD involvement. 9 patients had a high level of LDH. β<sub>2</sub>-microglobulin was high in 10 patients. Characteristics of the patients are summarized in Table 1. A total of 10 patients received HD-MTX with a concomitant intravascular chemotherapy as an initial treatment. 5 of them received 6 cycles of HD-MTX, 1 patient was stable after 3 cycles of HD-MTX, so RT was administered as a salvage regimen. After 3 cycles of HD-MTX, the disease became progressive in 1 patient and the patient died due to respiratory failure. 3 of the patients died due to sepsis after the second cycle of HD-MTX. In 2 patients, RT was planned to cranium in a fraction of 20 at a dose of 36 Gy in total.

#### b) Response to treatment

Of the remaining 4 patients, 1 was regarded as having a progressive disease and died due to respiratory failure. The rest 3 patients died due to sepsis after the second cycle of HD-MTX (these patients were included in the progressive disease group). RT treatment was administered as the initial treatment in 2 patients. One of these patients had low grade B cell lymphoma and died due to comorbid diseases on the 16th day of the treatment. The patients receiving RT had diffuse cell lymphoma that yielded partial remission. 10 patients additionally received 6 cycles of intraventricular chemotherapy. No recurrence was observed in the

study population. Toxicities included pancytopenia, infection, mucositis and neurotoxicity. 3 patients died as a result of sepsis due to severe neutropenia. Outcomes are summarized in Table 2.

#### c) Toxicity

Toxicity included grade 3/4 hematotoxicity (50%), and mucositis (20). Renal toxicity was observed in 1 patient while liver toxicity was present in 1 patient. These toxicities improved after HD-MTX and the treatment was not postponed due to toxicity. However, in 5 patients, grade 3/4 hematologic toxicity developed after HD-MTX. These patients were administered colony-stimulating factor and wide spectrum antibiotherapy. However, 3 patients died as a result of sepsis due to infection.

There was neurotoxicity proven by MRI only in one patient, but the patient did not clinically exhibit any neurologic pattern. The details about toxicity are outlined in Table 3.

## IV. DISCUSSION

PCNSL, which is an aggressive lymphoma with poor prognosis, is mostly incurable.<sup>17</sup> This retrospective study was conducted to evaluate the clinicopathological profiles and outcomes of the patients diagnosed with PCNSL at our institute. 14 cases were diagnosed with PCNSL between August 2010 and May 2016. In PCNSL, which is a condition occurring at all ages, the incidence rates reported in the sixth and seventh decades are higher in immunocompetent patients in the western countries.<sup>18,19</sup> In our study, the average age was 62 years while the youngest patient was 42 years old and the oldest one was 80 years old. The median age of the patients was 69 years and male-to-female ratio was 9/5. Bataille et al.<sup>18</sup> analysed PCNSL in 248 (121 males and 127 females) immunocompetent patients where the median age was 61 years. They suggested that this type of lymphoma occurred more commonly in men than women.<sup>20</sup> In our study, the number of male patients was higher.

Intra-cranial lymphomas are diagnosed using both morphological criteria and immunohistochemical studies. Most primary intra-cranial lymphomas are comprised of non-Hodgkin's B-cells. CSF analysis results in a cytological diagnosis in fewer than half of patients with B-cell PCNSL. Solitary lesions, which are most commonly located supra-tentorially, in the white matter of the frontal or parietal lobes or in the subependymal regions can be revealed by neuro-imaging modalities. Sarkar et al.<sup>21</sup> reported frontal lobe as the most common location in their study. In our study, 4 of the lesions were located in the parieto-occipital region. Lesions were localized at the parietal region in 2 patients, temporal region in 2 patients and occipital region in 1 patient. The other 2 lesions were in the frontal lobe, and one of these two lesions was located in

cerebellar region which is very rare localization. There were multiple lesions in 2 patients.

The vast majority of PCNSLs are DLBCL. In our study, 13 of the cases were classified as high grade DLBCL, a predominant histological type as shown in other studies, and 1 was classified as low grade lymphoma. In our study, none of the tumour cells involved the CSF and all the cases were immunocompetent with no HIV positive case.

Age and performance status are universally accepted as prognostic factors. Ferreri et al.<sup>22</sup> used multivariate analysis in a large cohort of patients with PCNSL, which is a new understanding in this area. They reported an independent association between OS and age, performance status, LDH serum concentration, CSF protein concentration and involvement of deep structures of the brain. A prognostic score, obtained by adding each of these variables (assigned a score of 0 or 1, if absent or present), was significantly correlated with survival and made it possible to distinguish low, intermediate and high risk groups. After analysing all of the patients, we observed that they all were in high risk group.

Treatment for intra-cranial lymphoma can include chemotherapy, RT, surgery and a combination of these treatment modalities.<sup>10</sup> In elderly patients, chemotherapy alone is preferred as it is as effective as and less neurotoxic than RT or chemoradiotherapy.<sup>23</sup> Introduction of MTX, which is a drug which penetrating the blood brain barrier effectively, has improved median survival from 10 to 16 months to more than 30 months.<sup>24</sup> In our study, the median OS was  $12.42 \pm 13.20$  months (min: 1 month, max: 48 months).

In order to minimize acute and late toxicities in the management of PCNSL, many studies have investigated the role of single-agent chemotherapy and deferred WBRT. MTX doses greater than  $1 \text{ g/m}^2$  are reported to be necessary for adequate delivery to the CNS.<sup>25</sup> Intraventricular chemotherapy aims to improve CSF drug delivery. Thus, many studies of PCNSL employed intrathecal/intraventricular chemotherapy. We believe that high dose MTX as a single dose agent combined with intrathecal/intraventricular chemotherapy is the best treatment modality in PCNSL management.

As a result, PCNSL affects mostly the 6th decade and DLBCL is the most commonly encountered pathological type. Although single agent treatment modalities are frequently used in the treatment of newly diagnosed PCNSL, comprehensive randomized studies are needed. However, single agent high dose MTX seems to be causing toxicity less. Due to its neurocognitive toxicity, RT is mostly used in only relapsed/refractory patients.

## V. ACKNOWLEDGMENTS

The authors declare that there is no conflict of interests regarding the publication of this paper.



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FIGURES LEGENDS

Table 1: Patient characteristics

	Total (n=14)	HD-MTX (n=10)	Nontreatment (n=2)	Radiotherapy (n=2)
<b>Age</b>				
Median (years)	62	56.4	58	68
Range (years)	42-80	42-80	58	61-75
<b>Gender</b>				
Female	5	3	1	1
Male	9	7	1	1
<b>Lesions</b>				
Single	12	9	1	2
Multiple	2	1	1	-
<b>Surgical procedure</b>				
Stereotactic biopsy	3	3	-	-
Open biopsy	1	1	-	-
Tumor resection	3	1	1	1
<b>Pathology</b>				
DBLCL	13	10	2	1
Other	1	-	-	1
<b>LDH</b>				
Elevated	9	6	1	2
Normal	5	4	1	-
<b>B-2 Microglobulin</b>				
Elevated	10	7	2	1
Normal	4	4	-	-
<b>CSF cytology</b>				
Negative	10	10	-	-
Positive	-	-	-	-
Not performed	4	-	2	2
<b>IELSG score:</b>				
0-1	2	2	-	-
2-3	5	3	2	-
4-5	7	5	-	2

\* HD-MTX, high-dose methotrexate; IELSG, international extra-nodal lymphoma study group; CSF, cerebrospinal fluid.

Table 2: Outcome of HD-MTX-based chemotherapy and radiotherapy in PCNSL

	HD-MTX (n=10)	Radiotherapy (n=2)	Tedavisiz (n=2)
Complete Remission	5/10 (50%)	0/2 (0%)	0/2
Partial Remission	-	1/2 (50%)	*Not evaluated
Progressive Disease	***3/10 (%20)	**Not evaluated	*Not evaluated
Stable Disease	2/10 (%25)	**Not evaluated	*Not evaluated

\* The patient has died at the 16<sup>th</sup> day of radiation therapy.

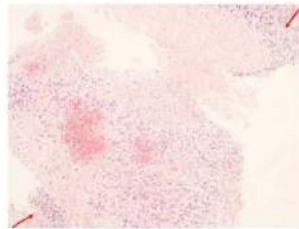
\*\* 2 patients died due to respiratory failure after the diagnosis.

\*\*\* 2 patients died due to sepsis after the 2nd cycle of HD-MTX treatment.



*Table 3:* Toxicity of HD-MTX-based chemotherapy and radiotherapy in PCNSL

	HD-MTX (n=10)	Radiotherapy (n=2)
<b>Anemia</b> (grade 3/4)	5 (50%)	0
<b>Thrombocytopenia</b> (grade 3/4)	5 (50%)	0
<b>Neutropenia</b> (grade 3/4)	5 (50%)	0
<b>Renal toxicity</b> (grade 3/4)	1	0
<b>Liver toxicity</b> (grade 3/4)	1	0
<b>Infections</b> (grade 3/4)	3(33%)	0
<b>Mucositis</b>	2 (20%)	1 (50%)
<b>Neurotoxicity</b>	1 (10%)	0
<b>Toxic Death</b>	3	0



*Figure 1:* Cerebellar tissue (red arrows) and large scattered atypical lymphocytes (H&E,x100). The tumour cells have round vesicular nucleus with multiple nuclei. The cells have scanty cytoplasm. There are characteristic lymphocytic infiltrates around vessels. [Immunohistochemically, LCA and CD20 positive; CD5, CD15, CD30, CD56, ER, PR, Chromogranin A, Synaptophysin, GFAP, CK7, GCDFP-15 and TTF-1 negative]

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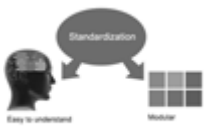
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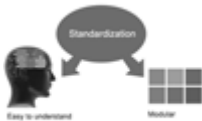


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Research articles: These are handled with small investigation and applications

Research letters: The letters are small and concise comments on previously published matters.

#### 5. STRUCTURE AND FORMAT OF MANUSCRIPT

The recommended size of original research paper is less than seven thousand words, review papers fewer than seven thousands words also. Preparation of research paper or how to write research paper, are major hurdle, while writing manuscript. The research articles and research letters should be fewer than three thousand words, the structure original research paper; sometime review paper should be as follows:

**Papers:** These are reports of significant research (typically less than 7000 words equivalent, including tables, figures, references), and comprise:

- (a) Title should be relevant and commensurate with the theme of the paper.
- (b) A brief Summary, "Abstract" (less than 150 words) containing the major results and conclusions.
- (c) Up to ten keywords, that precisely identifies the paper's subject, purpose, and focus.
- (d) An Introduction, giving necessary background excluding subheadings; objectives must be clearly declared.
- (e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition; sources of information must be given and numerical methods must be specified by reference, unless non-standard.
- (f) Results should be presented concisely, by well-designed tables and/or figures; the same data may not be used in both; suitable statistical data should be given. All data must be obtained with attention to numerical detail in the planning stage. As reproduced design has been recognized to be important to experiments for a considerable time, the Editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un-refereed;
- (g) Discussion should cover the implications and consequences, not just recapitulating the results; conclusions should be summarizing.
- (h) Brief Acknowledgements.
- (i) References in the proper form.

Authors should very cautiously consider the preparation of papers to ensure that they communicate efficiently. Papers are much more likely to be accepted, if they are cautiously designed and laid out, contain few or no errors, are summarizing, and be conventional to the approach and instructions. They will in addition, be published with much less delays than those that require much technical and editorial correction.



The Editorial Board reserves the right to make literary corrections and to make suggestions to improve brevity.

It is vital, that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

## Format

*Language: The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.*

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than  $1.4 \times 10^{-3} \text{ m}^3$ , or 4 mm somewhat than  $4 \times 10^{-3} \text{ m}$ . Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

## Structure

All manuscripts submitted to Global Journals Inc. (US), ought to include:

Title: The title page must carry an instructive title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) wherever the work was carried out. The full postal address in addition with the e-mail address of related author must be given. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining and indexing.

*Abstract, used in Original Papers and Reviews:*

### Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

### Key Words

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy and planning a list of possible keywords and phrases to try.

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art. A few tips for deciding as strategically as possible about keyword search:



- One should start brainstorming lists of possible keywords before even begin searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

*Acknowledgements: Please make these as concise as possible.*

#### References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

The Editorial Board and Global Journals Inc. (US) recommend that, citation of online-published papers and other material should be done via a DOI (digital object identifier). If an author cites anything, which does not have a DOI, they run the risk of the cited material not being noticeable.

The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

#### Tables, Figures and Figure Legends

*Tables: Tables should be few in number, cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g. Table 4, a self-explanatory caption and be on a separate sheet. Vertical lines should not be used.*

*Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.*

#### Preparation of Electronic Figures for Publication

Even though low quality images are sufficient for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit (or e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings) in relation to the imitation size. Please give the data for figures in black and white or submit a Color Work Agreement Form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution (at final image size) ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs) : >350 dpi; figures containing both halftone and line images: >650 dpi.



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*Figure Legends: Self-explanatory legends of all figures should be incorporated separately under the heading 'Legends to Figures'. In the full-text online edition of the journal, figure legends may possibly be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should notify the reader, about the key aspects of the figure.*

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Upon approval of a paper for publication, the manuscript will be forwarded to the dean, who is responsible for the publication of the Global Journals Inc. (US).

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The corresponding author will receive an e-mail alert containing a link to a website or will be attached. A working e-mail address must therefore be provided for the related author.

Acrobat Reader will be required in order to read this file. This software can be downloaded

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Proofs must be returned to the dean at [dean@globaljournals.org](mailto:dean@globaljournals.org) within three days of receipt.

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Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

#### TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

**1. Choosing the topic:** In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

**2. Evaluators are human:** First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

**3. Think Like Evaluators:** If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

**4. Make blueprints of paper:** The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

**5. Ask your Guides:** If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

**6. Use of computer is recommended:** As you are doing research in the field of Computer Science, then this point is quite obvious.

**7. Use right software:** Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

**8. Use the Internet for help:** An excellent start for your paper can be by using the Google. It is an excellent search engine, where you can have your doubts resolved. You may also read some answers for the frequent question how to write my research paper or find model research paper. From the internet library you can download books. If you have all required books make important reading selecting and analyzing the specified information. Then put together research paper sketch out.

**9. Use and get big pictures:** Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

**10. Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

**11. Revise what you wrote:** When you write anything, always read it, summarize it and then finalize it.



**12. Make all efforts:** Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

**13. Have backups:** When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

**14. Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

**15. Use of direct quotes:** When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

**16. Use proper verb tense:** Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

**17. Never use online paper:** If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

**18. Pick a good study spot:** To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

**19. Know what you know:** Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

**20. Use good quality grammar:** Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

**21. Arrangement of information:** Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

**22. Never start in last minute:** Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

**23. Multitasking in research is not good:** Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

**24. Never copy others' work:** Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

**25. Take proper rest and food:** No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

**26. Go for seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.





**27. Refresh your mind after intervals:** Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

**28. Make colleagues:** Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

**29. Think technically:** Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

**30. Think and then print:** When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

**31. Adding unnecessary information:** Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

**32. Never oversimplify everything:** To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

**33. Report concluded results:** Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

**34. After conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

## INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

### Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

### Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.



Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

**General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

- Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

- Use standard writing style including articles ("a", "the," etc.)
- Keep on paying attention on the research topic of the paper
- Use paragraphs to split each significant point (excluding for the abstract)
- Align the primary line of each section
- Present your points in sound order
- Use present tense to report well accepted
- Use past tense to describe specific results
- Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives
- Shun use of extra pictures - include only those figures essential to presenting results

**Title Page:**

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.



## Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript-- must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for brevity. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

## Approach:

- Single section, and succinct
- As an outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an abstract must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

## Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

## Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.



- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

#### **Procedures (Methods and Materials):**

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

#### **Materials:**

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

#### **Methods:**

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

#### **Approach:**

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

#### **What to keep away from**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

#### **Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently. You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.



## Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

### What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

### Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

### Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

### Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
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<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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