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Highlights

Patients with Hypertonic Disease

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#### GLOBAL JOURNAL OF MEDICAL RESEARCH: F Diseases Cancer, Ophthalmology & Pediatric

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# Sturge-Weber Syndrome in a 28-Year-old Tanzanian Female: A Case Report

By Sarah Shali Matuja, Maryam Amour, Evangelista Malindisa & William Matuja

#### Catholic University

*Abstract- Background:* Sturge Weber Syndrome is a sporadic neurocutaneous disorder of elusive etiology which is characterized by a vast continuum of manifestations ranging from neurological, cutaneous and ocular features. The main complications of the disorder include epileptic seizures, hemi paresis, and delayed neuropsychological development leading to poor quality of life.

*Case presentation:* We present a 28 years old female of African descent who was seen at our neurology outpatient clinic in Dar es Salaam, Tanzania with a chief complaint of relapsing generalized motor seizures for the past 1 month. She had been on Anti-Epileptic Drugs since birth with poor control. Physical examination revealed an obese lady with Port Wine Stain appearance on the left half of the head, face, and neck. She had reduced visual acuity on the left eye, dysphasia with severe right-sided spastic hemi paresis. Her Computed Tomography films revealed extensive gyral and sub cortical calcifications seen on the left posterior cerebral parenchymal also involving the parietal-temporal lobes.

Keywords: sturge weber syndrome, seizures, port-wine stain, angiomas.

GJMR-F Classification: NLMC Code: WL 356

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# Sturge-Weber Syndrome in a 28-Year-old Tanzanian Female: A Case Report

Sarah Shali Matuja <sup>a</sup>, Maryam Amour <sup>a</sup>, Evangelista Malindisa <sup>e</sup> & William Matuja <sup>a</sup>

Abstract- Background: Sturge Weber Syndrome is a sporadic neurocutaneous disorder of elusive etiology which is characterized by a vast continuum of manifestations ranging from neurological, cutaneous and ocular features. The main complications of the disorder include epileptic seizures, hemi paresis, and delayed neuropsychological development leading to poor quality of life.

Case presentation: We present a 28 years old female of African descent who was seen at our neurology outpatient clinic in Dar es Salaam, Tanzania with a chief complaint of relapsing generalized motor seizures for the past 1 month. She had been on Anti-Epileptic Drugs since birth with poor control. Physical examination revealed an obese lady with Port Wine Stain appearance on the left half of the head, face, and neck. She had reduced visual acuity on the left eye, dysphasia with severe right-sided spastic hemi paresis. Her Computed Tomography films revealed extensive gyral and sub cortical calcifications seen on the left posterior cerebral parenchymal also involving the parietal-temporal lobes. Her electroencephalography showed abnormal focal activity in keeping with a diagnosis of Sturge weber syndrome. The patient is currently on carbamazepine and clobazam with remarkable improvement attending regular follow-ups at our outpatient clinic.

*Conclusions:* Sturge weber syndrome is a rare congenital disorder presenting with a diverse spectrum of clinical manifestations. We present a case of delayed diagnosis thus recommending complete understanding of the disorder to clinicians in order to ensure early diagnosis since it offers opportunities to control for seizure-related complications leading to preserved quality of life.

*Keywords:* sturge weber syndrome, seizures, port-wine stain, angiomas.

#### I. Background

Sturge weber syndrome (SWS) is a sporadic neurocutaneous disorder of elusive etiology (1). It is characterized by a vast continuum of manifestations ranging from neurological, cutaneous and ocular features (2). In 1879, Sturge linked the dermatological and ophthalmic manifestations of the disorder to the neurological symptoms and signs, later in 1929 Weber described the radiographic changes associated with SWS (3). The estimated frequency is 1:50,000 live births yet experts believe more have the disorder, it is just undiagnosed (4). It has no racial predilection and has an equal male to female ratio (5). A proposed mechanism associated with SWS is a somatic mosaic mutation in the Guanine Nucleotide G Protein Q polypeptide gene (GNAQ) located at chromosome 9 which results in activation of several signaling cascades responsible for the syndromic manifestations of the disease (6,7).

Neurological malformations are characterized by presence of an ipsilateral leptomeningeal angioma responsible for the epileptic seizures, migraine like vascular headaches, hemiparesis, and mental retardation (8).

Facial Port wine stain (PWS), a dermo-capillary vascular malformation is the main cutaneous manifestation usually present at birth and its distribution involves the forehead and upper eyelid in the first (V1), second (V2) division as well as the third (V3) division of the trigeminal nerve (9,10). Ocular features include glaucoma or choroidal hemangiomas (11,12). They may also present with hypothalamic-pituitary disorders like growth hormone deficiency and central hypothyroidism (13,14).

Neuro imaging with either Magnetic Resonance Image or Computed Tomography scan (CT) is preferred to characterize the cerebral abnormalities which become apparent later in life (15). Treatment of SWS is usually conservative encompassing a combination of anti-epileptic drugs (AED) to ensure seizure control and management of glaucoma (16). In this report, we present a case of documented SWS in Tanzania with its classical clinical manifestations and neurological complications.

#### II. CASE PRESENTATION

A 28 years old female of African descent was seen for the first time at our neurology outpatient clinic in Dar es Salaam, Tanzania with a chief complaint of relapsing generalized motor seizures on daily basis for the past 1 month. She was known to suffer from epileptic-seizures and had been on Anti-Epileptic Drugs (AED) of unknown dosage since birth (phenobarbital and valproate) with irregular clinic visits due to challenges in distance from home to the health care facility. Her seizures were not well controlled which

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ultimately led to cognitive impairment, delayed motor milestone development which hindered her from attending school. She was the 4<sup>th</sup> born of 6 children and the other siblings were of good health.

On examination, she was obese with a hyper pigmented lesion extending from the left half of the head, face, and neck consistent with a PWS which was present since birth (figures 1 and 2). She had reduced visual acuity on the left eye ( $N_{26}$ ) probably due to glaucoma which was previously diagnosed during childhood and was treated medically. She had a poor understanding of spoken speech and was unable to communicate properly with severe right-sided spastic hemiparesis.

Her most recent brain CT films taken as an adult revealed extensive gyral and subcortical calcifications seen on the left posterior cerebral parenchymal extending to the left parietal and temporal regions (figures 3 and 4). Her electroencephalogram revealed an abnormal focal activity with normal thyroid and growth hormone assays. A diagnosis of SWS was made based on clinical and neuroimaging features. Phenobarbital and valproate were gradually stopped and the patient was subsequently commenced on carbamazepine 400mg twice daily (this was the maximum dose she could tolerate) and folic acid 5mg once a day. After 6 months of unsatisfactory response to monotherapy, clobazam 10mg twice daily was added. She has been seizure-free for 2 years and is followed up every 4 to 5 months at our neurology clinic in Dar es Salaam, Tanzania.

#### III. Discussion

SWS is a rare congenital neurocutaneous disorder. It is classified into three sub-types based on areas that are affected by residual blood vessels using the Roach scale (17). Type 1, which is the complete form includes the presence of both facial and leptomeningeal angiomas and patients may have glaucoma; type 2 is characterized by presence of facial angiomas alone and may have glaucoma and type 3 includes presence of an isolated leptomeningeal angioma; usually with no glaucoma (17). Based on the Roach criteria, our patient was the classical type 1 case.

Leptomeningeal vascular angiomas occur in 10 to 20% of cases, they are usually unilateral affecting the pia-arachnoid membrane and any region of the cerebral hemispheres (8). The parietal and occipital areas are most commonly affected leading to abnormal blood flow patterns causing cortical irritation as a result of ischemia, hypoxia, and gliosis (18). This leads to epileptic seizures and early onset seizures by the age of 2 has been associated with a poor prognosis leading to impaired cognition and mental retardation (19,20). Our patient had cerebral vascular angiomas involving the left temporal, parietal and occipital regions as evidenced by the CT brain films. Furthermore, she developed earlyonset seizures which were poorly controlled and neither was she on regular clinic visits which led to progressive neurological dysfunction including hemiparesis, speech and learning disabilities.

The presence of PWS seen in about 70% of patients typically involves the ophthalmic division of the trigeminal nerve ipsilateral to the cerebral angiomatosis (9). The lesion presents at birth and its appearance and size changes with age (16). Our patient presented with PWS observed since birth present on the ipsilateral side of the angiomatosis extending from the face, neck and left arm. Likewise, some patients parallel to our case may present with ocular abnormalities such as glaucoma as an ophthalmic complication presenting in 40% of patients from early childhood (20).

Treatment of SWS is variable and it entails a multi-disciplinary approach based on its diverse clinical picture. The mainstay in preventing progressive neurological damage is through early detection and vigorous control of seizures, leading to preserved quality of life (21).

The ideal first line AED that is commonly used in SWS is carbamazepine or oxcarbazepine monotherapy and an additional second-line therapy may be considered in resistant cases before opting for surgical interventions (20,22). Seizures in our patient cannot be described as resistant since there was a lack of proper monitoring of her initial regimen which she commenced since birth. She was not on regular clinics; her dosing regimen was not clear nor did she have any documented side effects. Remarkably however is that there was a significant improvement after the addition of clobazam to carbamazepine and the patient is currently seizure-free with regular clinic visits.

#### IV. Conclusions

SWS is a rare congenital developmental disorder presenting with a diverse spectrum of clinical manifestations. We present a case of delayed diagnosis, thus recommend a complete understanding of the disorder to health professionals to ensure early diagnosis and treatment since it offers opportunities to prevent and control for neurological deterioration. We also strongly emphasize on the use of a combination of AED with close monitoring of patients using carbamazepine and another second-line agent like clobazam to treat seizures in SWS which results in complete seizure remission.

List of abbreviations AED: Anti-Epileptic Drugs CT: Computed tomography PWS: Port wine stain SWS: Sturge weber syndrome Declarations

*Ethical approval:* Ethical approval was sought from the Directorate of Family Care Medical Clinic.

Consent to publication: Written informed consent was obtained from the patient and parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials: Not applicable.

*Competing interests:* The authors declare that they have no competing interests.

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Authors' contributions: SSM and WM took history, performed the physical examination, diagnosed and managed the patient. SSM wrote the initial draft of the manuscript. SSM, MM and EM critically reviewed the manuscript. All authors read and approved the final manuscript.

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FIGURE LEGENDS



Figure 1: Evidence of PWS extending from the left side of the head, face and neck



*Figure 2:* Showing evidence of PWS on the left face and neck



Figure 3: Extensive calcifications on the Left temporal and occipital cerebral hemispheres



Figure 4: Calcifications on the Left parietal and occipital cerebral hemispheres

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# Studying Signs of Diastolic Dysfunction of the Right Ventricle in Patients with Hypertonic Disease

By Saodat Yarmu khamedova, Feruz Nazarov, Xanuza Mahmudova, Nigora Vafoeva, Maxsuda Bekmuradova, Xudoyor Gaffarov, Doston Toirov, Murod Normatov, Suvon Yamatov & Munira Xusainova

Abstract- Hypertension is currently one of the most pressing medical problems. This is largely due to the fact that arterial hypertension, which is largely responsible for high cardiovascular morbidity, disability and mortality, and is also characterized by a wide prevalence. Early diagnosis of changes in the heart in patients with essential hypertension is of great practical interest, which allows timely preventive measures and treatment. As a rule, with arterial hypertension, the left ventricle is primarily and to a greater extent affected, since the main load falls on it from the very beginning of the disease. The analysis of parameters of diastolic function of the right ventricle was carried out depending on the level of rise in diastolic blood pressure between patients with mild and high arterial hypertension. At the same time, significant differences were revealed that related to the ratio of the maximum filling rate to the maximum expulsion rate.

Keywords: essential hypertension, arterial hypertension, diastolic dysfunction, right ventricle, echocardiography, maximum filling rate, maximum expulsion rate.

GJMR-F Classification: NLMC Code: WG 210



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## Studying Signs of Diastolic Dysfunction of the Right Ventricle in Patients with Hypertonic Disease

Saodat Yarmu khamedova <sup>°</sup>, Feruz Nazarov <sup>°</sup>, Xanuza Mahmudova <sup>°</sup>, Nigora Vafoeva <sup>©</sup>, Maxsuda Bekmuradova <sup>¥</sup>, Xudoyor Gaffarov <sup>§</sup>, Doston Toirov <sup>x</sup>, Murod Normatov <sup>v</sup>, Suvon Yamatov <sup>θ</sup> & Munira Xusainova <sup>ζ</sup>

Abstract- Hypertension is currently one of the most pressing medical problems. This is largely due to the fact that arterial hypertension, which is largely responsible for high cardiovascular morbidity, disability and mortality, and is also characterized by a wide prevalence. Early diagnosis of changes in the heart in patients with essential hypertension is of great practical interest, which allows timely preventive measures and treatment. As a rule, with arterial hypertension, the left ventricle is primarily and to a greater extent affected. since the main load falls on it from the very beginning of the disease. The analysis of parameters of diastolic function of the right ventricle was carried out depending on the level of rise in diastolic blood pressure between patients with mild and high arterial hypertension. At the same time, significant differences were revealed that related to the ratio of the maximum filling rate to the maximum expulsion rate. There was a tendency to an increase in the time of the fast filling phase of the contribution of the fast filling phase to the right ventricular diastole, which is due to the initial signs of diastolic dysfunction of the right ventricle with a decrease in the maximum filling rate and a moderate increase in the contribution of right atrial systole to right ventricular filling.

Keywords: essential hypertension, arterial hypertension, diastolic dysfunction, right ventricle, echocardiography, maximum filling rate, maximum expulsion rate.

#### I. INTRODUCTION

ypertension is currently one of the most pressing medical problems. This is largely due to the fact that arterial hypertension, which largely determines high cardiovascular morbidity, disability and mortality, and is also characterized by a wide prevalence. [1, 2]

Myocardial remodeling remains a significant factor worsening the course and prognosis of hypertension. While the remodeling of the left ventricle in hypertension has been studied rather well, the state of the right ventricle has received much less attention. Violations of the diastolic function of the right ventricle in patients with heart failure are an independent prognostic factor for survival, and the use of tissue Doppler ultrasonography reveals new informative parameters of diastolic dysfunction, as well as to prove its relationship

Author α: Samarkand State Medical Institute, Samarkand, Uzbekistan. e-mail: saodat.66@mail.ru with the development of pulmonary hypertension [1, 2, 4].

Despite the proven opinion about an increase in the risk of death from cardiovascular diseases with a combination of heart failure and arterial hypertension. myocardial remodeling in hypertensive disease against the background of concomitant heart failure is also insufficiently studied. Adaptive processes in the heart during the development of heart failure against the background of long-term arterial hypertension have their own characteristics, manifested in impaired diastolic function of the right ventricle. [5, 6, 7] preventive measures and treatment. As a rule, in this disease, the left ventricle is primarily and to a greater extent affected, and the main load falls on it from the very beginning of the disease [8, 9, 10]. It should be noted that the diastolic function, being a complex process consisting of numerous interrelated factors, depends on such indicators as: age, gender, body surface area, breathing phase, ventricular myocardial mass, heart rate, - and after load. [11, 12] With the help of various research methods, it has been established that the pancreas with hypertrophy also undergoes hypertrophy, impairments of its contractility and clinically expressed insufficiency develop. [12]

Purpose of the study: To study the diastolic function of the right ventricle in patients with different stages of hypertension and with concomitant heart failure of II-III functional classes.

#### II. MATERIALS AND METHODS

We examined 71 patients with essential hypertension. All examined were subjected to a comprehensive examination in order to exclude symptomatic hypertension and other diseases. The diagnosis of hypertension was made on the basis of the criteria proposed by the WHO expert committee. The study included patients with stage II-III hypertension - 31 women (43.66%) and 40 men (56.3%) (aged 25 to 63). The average age in the group was 50.3  $\pm$  4.6 years. For men, the average age was 43.4  $\pm$  4.9 years and for women, 52.7  $\pm$  4.9 years. The antihypertensive drugs were discontinued 24 hours before the start of the study.

Electro - ocardiographic examination was carried out in 12 conventional leads at a speed of 50 mm / sec.

Blood pressure was measured after at least 5 minutes of patient rest. Blood pressure was measured on the right brachial artery using the Korotkov method. The diagnosis of stage II hypertension was established in 46 patients. The average age of the patients was 42.3  $\pm$  4.2 years. Of these, 21 women (average age 44.7  $\pm$ 4.7 years) and 25 men (average age  $37.4 \pm 4.7$  years). The study excluded patients with diseases that significantly affect the systolic and diastolic function of the right ventricle, such as diabetes mellitus, obesity, chronic nonspecific lung diseases. tricuspid regurgitation more than grade II, tachycardia with heart rate more than 100 beats per minute and atrial fibrillation.

#### III. Results and Discussion

All patients showed signs of left ventricular hypertrophy on the ECG and the presence of hypertensive retinal angioretinopathy. Stage III hypertension was diagnosed in 25 patients with lesions of target organs. The average age of the patients was  $57.1 \pm 4.3$  years. Of these, 10 women (average age

55.9  $\pm$  4.6 years) and 15 men (average age 62.4  $\pm$  4.5 years). Of these, 7 patients (2 women and 5 men, average age 63.3  $\pm$  4.7 years) had a history of transient cerebrovascular accidents, the remaining 18 (6 women and 12 men, average age 56.2  $\pm$  5 , 3 years) documented coronary heart disease. The groups of patients with stage II and III hypertension did not differ significantly in terms of sex and age. The combination of hypertension and coronary heart disease and 8 men. mean age 54.3  $\pm$  2.6 years) and in 15 patients with hypertension stage III (60%) (7 women and 8 men, mean age 61.2  $\pm$  7.3 years the diagnosis of ischemic heart disease in hypertensive patients was made according to the criteria recommended by the WHO [2]. In the group of patients included in the study, the duration of hypertension was 13.4  $\pm$  3.2 years, the duration of a stable increase in blood pressure was - 9.7  $\pm$  3.8 years. 38 examined patients (53.5%) complained of headaches, 21 patients complained of dizziness, 29.5%), pain in the left side of the chest was observed in 30 patients (42.2%). The severity of heart failure in patients with various stages of hypertension is shown in Table 1.

*Table 1:* The severity of heart failure in hypertensive patients

	Heart failure Functional class I	Heart failure Functional class II	Heart failure Functional class III	Heart failure Functional class IV
Hypertonicdisease Stage II	20	24	2	-
Hypertonicdisease Stage III	2	13	10	-

The distribution of patients by age and severity of heart failure is shown in Table 2.

Table 2: Distribution c	f patients b	y age and	severity of	heart failure
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Patientage	Less than 39	40-49	50-59	60-69	Total
Numberofpatients	10	33	18	10	71
Heart failure Functional class I	8	10	2	2	22
Heart failure Functional class II	2	22	4	1	37
Heart failure Functional class III	-	1	-	7	12
Heart failure Functional class IV	-		-	-	0

Among the examined patients included in the study, the labile course of the disease was noted in 7 (9.8%), stable blood pressure values - in 64 (90.1%) patients.

According to the "Recommendations of the WHO Committee of Experts" [1,2], the examination included patients with mild, moderate and high arterial hypertension. Patients with a mild form of increased

blood pressure were 25 (35.2%), with a moderate form - 37 (52.1%) and high arterial hypertension - 9 patients (12.7%).

An objective clinical study in 26 patients (36.6%) revealed an expansion of the boundaries of the relative dullness of the heart to the left. And in almost all examined patients during auscultation, an accent of the II tone was heard by the aorta; in patients with



hypertension stage III, a tendency toward a decrease in the fraction of the right ventricle was determined. The rest of the clinical indicators between the subgroups practically did not differ. Comparative clinical

characteristics of patients depending on the degree of rise in diastolic blood pressure are shown in Table 3. Indicators of systolic function of the right ventricle did not differ significantly between the subgroups.

	Mild (n = 25)	Moderate (n = $37$ )	High(n = 9)
Patientage	63,3± 5,3	65,3± 12,3	68,4± 13,7
Durationofillness	13,8+6,5	14,7 ±3,6	15,8±7,8
Duration of a stable flow	9,7±4,5	9,9±5,6	10,2±4,6
Systolic blood pressure	153,5±8,7	168,6±9,7	195,6±9,4
Diastolicbloodpressure	98,6+7,8	110,8±4,7	195,8±4,8
Heartfailurefunctionalclass	1,9±0,3	1,8±0,3	2,0±0,4
Rightventricularejectionfraction,%	55,4±8,7	66,7±10,8	58,5±7,7
Stroke volume of the right ventricle, ml	62,1±5,3	57,6±4,7	53,3±5,6

Table 3: Clinical characteristics of patients with varying degrees of rise in diastolic blood pressure

The analysis of the parameters of the diastolic function of the right ventricle was carried out depending on the level of rise in diastolic blood pressure between patients with mild and high arterial hypertension. At the same time, significant differences were revealed that related to the ratio of the maximum filling rate to the maximum expulsion rate with a tendency to an increase in the time of the fast filling phase, the contribution of the fast filling phase to the diastole of the right ventricle, which was due to the initial signs of diastolic dysfunction of the right ventricle with a decrease in the maximum speed filling and a moderate increase in the contribution of the right atrial systole to the filling of the right ventricle. The indices of relaxation and filling of the right ventricle between patients with mild and moderate increases in blood pressure did not differ significantly, except for patients with a moderate increase in diastolic blood pressure. When analyzing the diastolic function of the right ventricle, depending on the stage of hypertension, the following indicators were revealed (Table 4). Significant differences between the subgroups of patients with essential hypertension concerned only the ratio of the maximum filling rate to the maximum expulsion rate, which significantly decreased in stage II hypertension.

Table	4: Indicators of diastolic function of the right ventricle in patients with varying degrees of rise in diastolic
	blood pressure

	Mild (n = 25)	Moderate ( $n = 37$ )	High(n = 9)
Maximum filling speed, ml / sec	280,8±12,7	300,6+15,8	299,7±17,6
Maximum expulsion rate, ml / sec	300,5±13,6	301,4±13,7	298,6±10,7
Time to reach the maximum filling rate, msec	334,3+35,8	320,7±36,9	321,9±34,9
Time to reach the speed of maximum expulsion, msec	140,4±18,9	144,7±11,6	140,8+18,8
Time to reach the speed of maximum filling, correlated to the duration of the cardiac cycle,%	34,4±14,8	37,7±11,9	36,8±15,7
Time to reach the speed of maximum filling, correlated to the duration of diastole,%	35,3±15,5	35,6±12,6	35,5±14,6
The ratio of the maximum filling rate to the maximum expulsion rate, units	0,84±0,08	0,96±0,08	0,95±0,06
Contribution of the first third of diastole to filling the right ventricle,%	15,3±8,6	15,6±6,6	16,6±9,6
Fastfillingphasecontribution,%	42,5±6,9	32,7±6,8	35,6±7,5
Contribution of right atrial systole to right ventricular filling,%	15,9±5,8	14,8±6,6	14,7±4,8
End-diastolic volume of the right ventricle, ml	125,5±9,7	127,9±8,9	135,8±8,8

	Hypertension II stage (n=46)	Hypertension Illstage(n=25)	Control
Maximum filling speed, ml / sec	300,3+14,6	340,7± 15,8	302,4±15,8
Maximum expulsion rate, ml / sec	314,7±135	300,5+11,2	302,5±14,2
Time to reach the maximum filling rate, msec	330,3±42,6	189,9±36,8	320,5±15,6
Time to reach the speed of maximum expulsion, msec	314,7±13,5	143,5±13,7	147,7±8,6
Time to reach the speed of maximum filling, correlated to the duration of the cardiac cycle,%	330,3±42,7	42,7±11,8	20,8±16,7
Time to reach the maximum filling rate in relation to the duration of diastole,%	138,5±14,7	41,4±12,3	25,5+15,6
The ratio of the maximum filling rate to the maximum expulsion rate, units	24,3±13,8	1,04+0,04	0,93+0,03
Contribution of right atrial systole to right ventricular filling,%	24,3±147	23,7±8,4	18,6+10,6
Fastfillingphasecontribution,%	0,88±0,08	40,6±6,4	40,6±64
Contribution of right atrial systole to filling of the right ventricle,%	15,3±8,6	14,7±6,7	12,7±3,7
End-diastolic volume of the right ventricle, ml	37,5±8,7	135,8±9,9	125,6±5,8
Stroke volume of the right ventricle, ml	13,5±7,8	46,7±5,7	52,3±4,7

Table 5 Indicators of diastolic function of the right ventricle at different stages of hypertension

Further study of the diastolic function in patients with stage II hypertension revealed that 31 patients (40.8%) had a "pseudo-normal" type of diastolic disorders, which consists in approaching the normative indicators of the maximum filling rate, as well as in normalizing the contribution of the system atrial tolas (Table 8).

*Table 6:* Indicators of diastolic function of the right ventricle in patients with hypertension stage II, depending on the type of diastole disorders

Indicator	Moderate Relaxation Disorders ( $n = 15$ )	Pseudo-normaltype (n=31)	Control
Maximum expulsion rate, ml / sec	300,8+12,5	295,9±12,5	302,5+14,1
Maximum filling speed, ml / sec	190,4±13,6	300,3±12,3	302,4±15,8
Time to reach maximum expulsion speed, msec	145,7±6,9	144,6+4,9	147,7±8,9
Time to reach the maximum filling rate, msec	323,4±12,6	317,3±13,7	320,5+15,6
Time to reach the maximum filling rate in relation to the duration of diastole,%	24,5±14,5	25,7±14,6	25,5±15,6
Maximum filling speed / maximum expulsion speed, units	0,73±0,06	0,94+0,06	0,93±0,03
Contribution of the first third of diastole to the filling of the right ventricle,%	16,8±9,8	8,3±4,4	18,3±6,2
Contribution of fast filling to filling of the right ventricle,%	41,5±4,5	42,6±7,3	40,6+6,5
Contribution of right atrial systoles to filling of the right ventricle,%	14,4±5,8	11,3± 4,9	12,7±3,8
End-diastolic volume of the right ventricle, ml	128,7±9,8	124,8±8,8	125,6±5,8
End-diastolicvolume, ml	55,6±6,4	53,6±5,4	52,3+4,7

Thus, the diastolic function of the left ventricle depends on the level of blood pressure and / or the

presence of myocardial hypertrophy, but also on the neurohumoral changes that are characteristic of the



initial stages of hypertension. The revealed data show the processes of myocardial hypertrophy not only of the left, but also of the right ventricle. The development of diastolic disorders on the part of the right ventricle begins with a decrease in the maximum filling rate and a compensatory increase in pressure in the right atrium. These disorders are significant in comparison with the pseudo-normal type of diastolic dysfunction. The significant nature of these changes and the relatively high number of patients with this type of diastolic disorders among patients with stage II essential hypertension cause a tendency towards a decrease in the maximum filling rate in stage II hypertension, which led to a significant decrease in the index of maximum filling rate / maximum expulsion rate in these data. sick.

The pseudonormal type of right ventricular dysfunction is associated with an increase in maximum

filling rate. The increase in the maximum filling speed is of a compensatory nature, allowing to overcome the rigidity of the right ventricle. In addition, this type of diastolic dysfunction was associated with a shortening of the time of isovolumic relaxation. With the development of stage III HD, there is a significant predominance of patients with a restrictive type of diastole disorder (Table 9). At the same time, there was an increase in the maximum rate of filling and a decrease in the parameters of the contractile ability of the right ventricle. The index of the ratio of the maximum filling rate to the maximum expulsion rate significantly increased. In patients with stage III hypertension, the formation of a restrictive type of diastolic disorders also influenced the temporal indices of diastolic disease. For example, there was a tendency to an increase in the time of the rate of maximum filling and expulsion.

Table 7: Indicators of diastolic function of the right ventricle in patients with hypertension stage III,	depending on the
type of diastole disorders	

	Pseudo-normaltype $(n = 4)$	Restrictivetype $(n = 21)$	Control
Maximum expulsion rate, ml / sec	296,8+13,5	167,5+13,5	302,5+14,1
Maximum filling speed, ml / sec	302,4±19,3	335,3±15,2	302,4+15,8
Time to reach the speed of maximum filling, correlated to the duration of the cardiac cycle,%	19,6±13,3	24,6+14,8	20,8±16,7
Time to reach the speed of maximum maximum expulsion, msec	144,6+7,9	154,4±8,4	147,7+8,9
Time to reach the speed of maximum maximum filling, msec	318,4±13,6	330,5±14,8	320,5±15,5
Time to reach the maximum filling rate in relation to the duration of diastole,%	25,6±17,7	30,9+13,8	25,5±15,6
Maximum filling speed / maximum expulsion speed, units	0,96±0,08	1,13±0,05	0,93±0,03
Contribution of the first third of diastole to filling the right ventricle / 3,%	8,5±4,6	19,8±8,7	18,6+6,3
Contribution of the fast filling phase to filling the right ventricle,%	41,5±8,4	41,7+5,4	40,6±6,7
Contribution of right atrial systole to right ventricular filling,%	12,5+ 9,8	16,8±7,8	12,7±3,8
End-diastolic volume of the right ventricle, ml	124,8±8,9	121,8+7,8	125,6±5,8
Stroke volume of the right ventricle, ml	54,6+5,7	46,3±6,8	52,3±4,7

The indicator of the ratio of the maximum filling rate to the maximum expulsion rate is an indicator of diastolic dysfunction of the right ventricle, depending on the stage of hypertension. The predominance among patients with stage III hypertension of patients with restrictive type of diastole disorders led to a significant increase in the index of the ratio of the maximum filling rate to the maximum expulsion rate, while in patients with stage II hypertension, its decrease was noted.

For patients with stage II hypertension, it was  $1.54 \pm 0.5$ , and for patients with stage III hypertension -  $2.6 \pm 0.4$ . There were no significant differences in the stage of insufficiency of the maximum rate of expulsion of blood circulation between the groups, however, in

order to minimize the effect of developing heart failure on the considered indicators, in the future, the analysis of diastolic disorders will be carried out in each subgroup separately.

#### IV. CONCLUSION

Thus, with the addition of cardiac insufficiency, patients at various stages of hypertension develop more severe diastolic dysfunction of the right ventricle, in some cases, the character of a restrictive nature. In patients with severe heart failure, a decrease in the contractility of the right ventricle is revealed, which consisted in a reliable, decrease, a tendency to a decrease in the stroke volume and an increase in the bed-diastolic volume of the right ventricle.

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### Impact of COVID-19 Attributable Deaths on Longevity, Premature Mortality and DALY: Estimates of USA, Italy, Germany and Sweden

By Sanjay K Mohanty, Manisha Dubey, Udaya S Mishra & Umakanta Sahoo

*Abstract- Background*: In a short span of four months, the COVID-19 pandemic has added over 0.6 million deaths worldwide, which are untimely, premature and unwarranted. The USA, Italy, Germany and Sweden are four worst affected countries, accounting to over 40% of COVID-19 deaths globally. The main objective of this study is to examine the impact of COVID-19 attributable deaths on longevity, years of potential life lost (YPLL) and disability adjusted life years (DALY) in USA, Italy, Germany and Sweden.

*Data and Methods:* Data from United Nation Population Projection, Statista and centre for disease control and prevention were used in the analyses. Life expectancy, YPLL and DALY were estimated under four scenarios; no COVID-19 deaths, actual number of COVID-19 death as of 20<sup>th</sup> July, 2020 and anticipating COVID-19 death share of 6% and 10% respectively.

Keywords: COVID-19, mortality, life expectancy, USA, italy, germany, sweden.

GJMR-F Classification: NLMC Code: WF 140

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## Impact of COVID-19 Attributable Deaths on Longevity, Premature Mortality and DALY: Estimates of USA, Italy, Germany and Sweden

Sanjay K Mohanty<sup>a</sup>, Manisha Dubey<sup>o</sup>, Udaya S Mishra<sup>o</sup> & Umakanta Sahoo<sup>o</sup>

Abstract- Background: In a short span of four months, the COVID-19 pandemic has added over 0.6 million deaths worldwide, which are untimely, premature and unwarranted. The USA, Italy, Germany and Sweden are four worst affected countries, accounting to over 40% of COVID-19 deaths globally. The main objective of this study is to examine the impact of COVID-19 attributable deaths on longevity, years of potential life lost (YPLL) and disability adjusted life years (DALY) in USA, Italy, Germany and Sweden.

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*Results:* The COVID-19 attributable deaths have lowered the life expectancy by 0.6 years in USA, 0.5 years in Italy and Sweden and 0.1 years in Germany. The loss of YPLL was 1.59, 0.13, 0.26 and 0.02 million in USA, Italy, Germany and Sweden respectively. The DALY (per 1000 population) due to COVID-19 was 5.4 in USA, 6.3 in Italy, 1.2 in Germany and 0.6 in Sweden. Compression in life expectancy and increase in YPLL and DALY may intensify further if death continues to soar.

*Conclusion:* COVID-19 has a marked impact on mortality. Reduction in longevity premature mortality and loss of DALY is higher among elderly.

Keywords: COVID-19, mortality, life expectancy, USA, italy, germany, sweden.

#### I. INTRODUCTION

OVID-19 attributable deaths are soaring each day in most of the countries with uncertainties over projected numbers, infection fatality ratio, development of a vaccine and possible end of pandemic. Globally, with over 16 million confirmed infections and additional deaths of over 650 thousand by end of July, 2020, the COVID-19 attributable deaths accounts for 1% of total all-cause mortality. If the COVID-19 mortality continues with same pace, the life expectancy would begin to shrink by end of the year though the survival threat is more among the elderly and the chronically ill. Rapid spread of the infection as well as its associated fatality may well be due to novel disease, lack of medical know how, ill-prepared health care system, crowding in urban cities, administrative inefficacy, demographic and social determinants etc.

The case fatality ratio (CFR) is a crude measure of mortality, underestimate the mortality impact of COVID-19. An alternative CFR with 14 days' delay depicts at least twice higher mortality than CFR [1]. The mortality impact of COVID-19 is higher than many other disease [2].The standardized metrics such as disability adjusted life years (DALY) and years lost due to disability (YLD) are suggested to infer infection fatality by age [3].

Considerable attempts are made on tracing future trajectories, estimation of infection and fatality rate and risk factors of COVID-19 [4-12].Demographic structure, co-morbidities and health-care burden explain COVID-19 attributable mortality to some extent [13-15]. Most common observation made as regard COVID-19 fatality is its greater risk among elderly and people with co morbidities including hypertension, diabetes, cardiovascular disease, myocardial injury [4,16-22]. The Diamond Princes cruise ship study of Japan, a standard estimate of infection, estimated the overall case fatality ratio of 2.6% as against the same being 13% among the older aged 70 and above [23].

Inadequate testing and misclassification of deaths by cause underestimate the extent of COVID-19 deaths. In USA, the excess deaths due to pneumonia and influenza raise an apprehension as regard missclassification of COVID-19 deaths in the absence of adequate testing [24]. In Italy, 54% deaths were COVID-19 making for attributed to case а misclassification of cause of death. The COVID-19 attributable mortality has potential to reduce life expectancy in India and seasonal life expectancy in Italy [25-26]. In United States, 1 million deaths from COVID-19 would increase mortality by one-third and reduction in period life expectancy by 3.9 years in 2020 [27].

Mortality impact of COVID-19 is higher in urban counties and the social determinants are significant

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predictors of its mortality [28]. High and low fatality due to COVID-19 attributed to density and age structure in terms of elderly in UK [29]. Demographic vulnerability of COVID-19 mortality is lower in younger countries in Sub-Saharan Africa than the industrialized countries [30]. The spread of infection and mortality depends on containment measures, health system response and micro-management of epidemic which may alter reproduction number [31].

By April 2020, the case fatality rate varied from 2.2% in South Korea to 13.0% in Italy. USA, Italy, Sweden and Germany were worst hit countries by the pandemic. By end of May 2020, USA had over 1.8 million confirmed cases and over 106 thousand deaths. About 80% of deaths occurred among adults aged 65 years or more [16]. In Italy, the CFR increased from 4.2% to 13.0% within 43 days and 90% of the change was due to increasing age specific case fatality rates [32]. In Italy, USA and Germany, estimated cases of infections are 6 times, 2 times and 1.2 times higher than the number of confirmed cases, respectively [33].

Existing studies of the pandemic on fatality is limited. Given its rise in intensity it becomes pertinent to gauge impact of COVID-19 attributable mortality on longevity, premature mortality and DALY. This will answer questions like "Would additional deaths due to COVID-19 reduce longevity and increase premature mortality and DALY".

#### II. DATA AND METHODS

We have analysed four worst affected countries; namely USA, Italy, Sweden and Germany that accounts over 40% of all COVID-19 attributable deaths worldwide. The selection of country is guided by the availability of age-specific infection and mortality data and severity of infection. Estimates are provided under four scenarios; no COVID-infection, COVID-infection as of 20<sup>th</sup> July, 2020 and estimates under 6% and 10% COVID-19 death share. Population and mortality data by age group for 2020 were obtained from the United Nation Population Projection [34]. The total deaths obtained from UN projection are estimated deaths in the absence of COVID-19 infection. The age specific COVID-19 attributable deaths for USA is collected from Centres for Disease Control and Prevention [35] and that for Italy, Germany and Sweden is taken from Statista [36-38]. The total number of confirmed cases and deaths for each country is collected from world meter website [39]. We have redistributed the total deaths available from world meter as per age distribution of deaths for which age data was available.

Under the assumption that the estimated deaths without COVID-19 and deaths due to COVID-19 are mutually exclusive, we have added these deaths to derive age specific death rate (number of deaths per 1000 population). The age specific case fatality ratio

(ASCFR) was computed for Italy and Sweden from given data. In case of Germany, the age group of number of infections were not uniform and deaths were available for 0-9, 10-19, 20-49, 50-69 and 70-89. We have redistributed the deaths as per population distribution in 10-year age group. In case of USA, we have used the ASCFR of Diamond Cruise Study that had constant rate (0.2) till age 35 beyond which we have taken the age group close to nearest age group [23].

#### III. Methods

Abridged life tables, estimation of years of potential life lost (YPLL) and disability adjusted life years (DALY) are used in the analyses. Estimates are based on the assumptions that COVID-19 attributable deaths are additional deaths that would have been avoided in absence of COVID-19 infection. The probability of death has been constructed from age specific death rate (ASDR). The 10-year abridged life table is used to estimate the life expectancy and other mortality estimates. Estimates are provided under four scenarios. Scenario 1 provides the deaths as estimated from UN population prospects and labelled as deaths without COVID-19. Scenario 2 considers COVID-19 deaths accounting for 6% of total deaths while scenario 3 would increase the death share to 10% of total deaths by the end of the year. Expected deaths due to COVID-19 are distributed in accordance with the age distribution of COVID-19 as of date. A brief description of YPLL and DALY estimation is given below.

#### a) Years of Potential Life Lost (YPLL)

The YPLL is a summary measure of premature mortality that estimates the average years a person would have lived had he or she not died prematurely. It gives higher weight to the deaths occurring at younger ages and lower weight to the deaths at higher ages [40-41]. YPLL is estimated as:

$$YPLL = \sum_{i=0}^{\infty} d_i * L_i$$

where,  $L_i$  is the life expectancy at age i and  $d_i$  is the number of deaths at age i. The deaths are weighted by life expectancy at each age.

#### b) Disability Adjusted Life Years (DALY)

DALY measures the health of a population by combining data on mortality and non-fatal health outcomes into a single number. The DALY measures health gaps as opposed to health expectancies. It measures the difference between a current situation and an ideal situation where everyone lives up to the age of the standard life expectancy, and in perfect health. It combines in one measure the time lived with disability and the time lost due to premature mortality:

$$DALY = YLL + YLD$$

where, YLL= years of life lost due to premature mortality and YLD= years lived with disability.

We have calculated YLL and YLD with discounting rate of 3% where discounting health with time reflects the social preference of a healthy year now, rather than in the future. The value of a year of life is generally decreased annually by a fixed percentage. For many years, a discount rate of 5% per annum has been standard in many economic analyses of health and in other social policy analyses, but recently environmentalists and renewable energy analysts have argued for lower discount rates for social decisions. The World Bank Disease Control Priorities study and the GBD project both used a 3% discount rate, and the US Panel on Cost-Effectiveness in Health and Medicine recently recommended that economic analyses of health also use a 3% real discount rate to adjust both costs and health outcomes [42].

The YLL is estimated as:

$$YLL = \frac{N}{r}(1 - e^{-rL})$$

where, N = number of deaths

L= Life expectancy at age of death

r= discount rate (we have also used 3% discount rate)

$$YLD = \frac{\left(I * DW * L * (1 - e^{-rL})\right)}{r}$$

where, I= number of incidence/prevalence cases. For acute diseases, incidence is considered same as prevalence

DW= disability weight (a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead)

L= duration of disability

r= discount rate

As COVID-19 is a novel disease, its disability weight is not available. Since COVID-19 is a severe infectious disease having acute period, we have used the disability weight of 0.133 for Infectious disease (acute episode, severe category) as proxy for COVID-19 [43]. The duration of disability of 60 days is used because the patients of COVID-19 have been hospitalized for on average 30 days and after discharge and quarantined for 14-28 days approximately.

#### IV. Results

Table 1 presents the key indicators of COVID-19 attributable mortality in four countries under study. With additional 1,43,504 deaths in USA, 35,058 deaths in Italy, 9168deaths in Germany and 5639 deaths in Sweden in a span of about seven months, the share of COVID-19 deaths amounts to 4.8% of total deaths in USA, 5.2% in Italy, 1.0% in Germany and 5.8% in Sweden. The COVID-19 attributable deaths can be considered as additional deaths avoidable without this infection. The case fatality ratio was very high in Italy (14.3) followed by Sweden (7.2) and Germany (4.5). The pandemic has infected at least 1.2% of the population in USA, 0.4% in Italy, 0.8% in Sweden and 0.2% in Germany. The COVID-19 attributable deaths has already lower life expectancy by 0.6 years for USA, 0.5 years each in Italy and Sweden and 0.1 years in Germany. At 10% share, the reduction in life expectancy would be 1.2 years for USA, 1 years for both Italy and Germany and 0.9 years for Sweden.

Fig 1 shows the reduction in life expectancy under varying scenarios of COVID-19 attributable deaths in USA, Italy, Germany and Sweden. Estimates suggest that the life expectancy is already lowered by 0.6 years in USA, 0.5 years each in Italy and Sweden and 0.1 years in Germany due to COVID-19 attributable deaths. In case of the COVID-19 attributable deaths would amount to 6% of total deaths in each country, the life expectancy at birth would reduce by 0.8 years in USA, 0.6 years each in Italy and Germany and 0.5 years in Sweden. The additional deaths due to COVID-19 results in a rise in CDR from 10.5 to 11.1 in Italy and this would rise to 11.6 with the COVID-19 death share rising to 10%. In case of USA, it has also increased from 8.6 to 9.5 with 10% share of COVID-19 death and the pattern is similar in Germany and Sweden as well.

Table 2 and 3 presents the estimates of life expectancy under varying scenarios of COVID-19 attributable deaths in USA, Italy, Germany and Sweden. Estimates from life table with and without COVID-19 for these four countries exhibit the changing age-specific survival patterns. The life expectancy for 2020 was 79.5 years in USA, 83.6 years in Italy, 81.5 years in Germany and 82.7 years in Sweden.

Table 4 and 5 shows the age specific assessment of Years of potential life lost (YPLL) under varying scenario of COVID-19 death share in USA, Italy, Germany and Sweden. While YPLL without COVID-19 was 55.2 million in USA, 8.9 million in Italy, 14.4 million in Germany and 1.3 million in Sweden, COVID-19 has added 1.55 million, 0.48 million, 0.12 million and 0.06 millions of YPLL in USA, Italy, Germany, and Sweden, respectively. Rate of YPLL (per 1000 population) is highest in Italy (7.9) followed by USA (7.1) and Sweden (6.4). With rising share of COVID-19 deaths to the tune of 6% and 10%, The share of YPLL on this count will rise from 7.1 to 8.8 and 14.3 per 1000 population, respectively in USA. Similar pattern has been observed for Italy, Germany and Sweden. Higher age-groups (45 years and above) are contributing more than 70% of YPLL in all the countries.

Table 6 and 7 shows the estimated DALY under varying scenarios of COVID-19 attributable deaths in USA, Italy, Germany and Sweden. The estimated DALY at current share of attributable COVID-19 deaths is 1.80 million in USA, 0.38 million in Italy, 0.10 million in Germany and 0.05 million in Sweden. At 6% share of attributable COVID-19 deaths, DALY for all ages would be 2.23 million in USA, 0.44 million in Italy, 0.60 million in Germany and 0.05 million in Sweden. The COVID-19 attributed loss has increased the DALYs by 6.3 per 1000 population in Italy, 5.4 in USA, 1.2 in Germany and 0.6 in Sweden. If COVID-19 attributable death accounts 6% death share, the DALYs would be 7.2 per 1000 population in Italy, 6.7 in USA, 7.1 in Germany and 0.7 in Sweden. Similarly, when COVID-19 accounts 10% death share, DALYs is 12.0 per 1000 population in Italy, 11.2 in USA, 11.9 in Germany and 1.1 in Sweden. Among all the four countries, the population 70 years and above account more than three-fourth contribution in DALY while younger ages have relatively low contribution in all the scenarios.

#### V. DISCUSSION AND CONCLUSION

The COVID-19 pandemic is one of the worst ever misery posed to mankind. While epidemics in the past have gripped limited geographical boundaries, the COVID-19 has engulfed the entire world within a brief period of four months with a reasonable degree of spread potential. Apart from threat to human life, its containment measures have led to economic loss and generated psychological scare among individuals, households, community and the nation at large. The COVID-19 pandemic has paralysed the economic activities, deepened the global recession and has assumed a crisis proportion worldwide. Given the scale and intensity of this pandemic, this is first attempt in our knowledge to assess the mortality attributed to COVID-19 in four worst affected countries. Such an assessment involves the extent of reduction in life expectancy, person year life lost and DALY that are yet to be made available so far. Selection of countries are primarily based on the extent of severity of the pandemic and availability of data but the exercise can very well be replicated elsewhere. The following are the salient findinas.

First and foremost. COVID19 induced fatalities have undoubtedly contributed towards rise in the overall mortality rate in all four countries. The death rate has increased from 8.6 without COVID-19 to 9.5 with COVID-19 in USA, from 10.5 to 11.6 in Italy, 11.0 to 12.1 in Germany and 9.1 to 10.0 in Sweden. Second, the life expectancy has compressed by 0.6 years in USA, 0.5 years each in Italy and Sweden and 0.1 years in Germany. Within a few months, the COVID-19 attributable death share amounts to about 5% each in USA and Italy, 1% in Germany and 6% in Sweden. If this trend of mortality continues till end of the year, reduction in life expectancy would be substantial in these countries. Third, most of the COVID-19 deaths are unwarranted, un timely and premature. COVID-19 attributable deaths have already added 1.5 million, 0.5 million, 0.1 million and 0.06 millions of YPLL in USA,

Italy, Germany, and Sweden, respectively. Fourth, with less than 1% infection, the DALY a from COVID-19 was 5.4 per thousand populations in USA, 6.3 in Italy, 1.2 in Germany and 0.6 in Sweden. If the spread of COVID-19 goes unabated, the loss of DALY would be similar to high fatality disease.

These findings are markers of tragedy experienced in countries ranked high in the level of human development, higher income level and are said to be having a better health care system. Hence the failure of preparedness to confront this pandemic by the developed world exposes our vulnerability to emerging infection of similar kind in future. In the absence of a vaccine as well as no systematic medical intervention, the only way out is the containment of its spread or developing a herd immunity in due course. At present great efforts are made by national and local government for management and control of pandemic by diverting the resources (financial and physical) for health care and lock down measures.

We acknowledge that the COVID-19 attributable deaths are to some extent underestimated due to lack of comprehensive testing, under-reporting and misclassification of COVID-19 deaths in these countries. Despite these limitations, these estimates of mortality pattern do signals about its long-term implications towards structural and compositional balance of population across world regions. Though it is very early to gauge its final impact on population structure and composition, its persistence with its virulence unless curbed by introduction of an effective vaccine and means of cure may well change the world order to a significant extent.

#### Conflict of interest

All authors have indicated no potential conflicts of interest to disclose.

#### Financial disclosure

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Summary Indicators	USA	Italy	Germany	Sweden
Total Population in million (2020)	331.0	60.5	83.9	10.1
Estimated number of annual deaths without COVID-19 (2020)	2830600	633800	923800	91200
Number of deaths with COVID-19 (As of 20th July)	143504	35058	9168	5639
Total Deaths including deaths due to COVID-19	2974104	668858	932968	96839
COVID-19 death as a share of total deaths as of 20th July 2020	4.8	5.24	0.98	5.82
Case-fatality ratio	3.7	14.33	4.51	7.23
Total number of COVID-19 infection as of 20th July, 2020	3925863	244624	203334	78048
Infection rate	1.2	0.40	0.24	0.77
Estimated Life expectancy without COVID-19 (years)	79.5	83.6	81.5	82.7
Reduction in life expectancy without actual number COVID-19 deaths (in Years)	0.6	0.5	0.1	0.5
Reduction in life expectancy without actual number COVID-19 deaths accounting to 6% (in Years)	0.8	0.6	0.6	0.5
Reduction in life expectancy without actual number COVID-19 deaths accounting to 10% (in Years)	1.2	1.0	1.0	0.9

Table 1: Summary indicators of population and COVID-19 attributable mortality indicators in USA, Italy, Germany and Sweden, 2020

Table 2: Life expectancy under varying scenarios of COVID-19 attributable mortality in United States of America (USA), 2020

Age group	Life expectancy without COVID-19	Life expectancy at current COVID-19 share of 4.8%	Life expectancy at current COVID-19 share of 6%	Life expectancy at current COVID-19 share of 10%
0-1	79.5	78.9	78.7	78.3
1-4	78.8	78.2	78.0	77.6
5-14	74.9	74.3	74.2	73.7
15-24	65.0	64.4	64.3	63.8
25-34	55.5	54.9	54.7	54.3
35-44	46.2	45.6	45.4	44.9
45-54	37.0	36.4	36.2	35.8
55-64	28.3	27.8	27.6	27.2
65-74	20.5	20.0	19.8	19.4
75-84	13.3	12.8	12.7	12.4
85+	7.6	7.2	7.2	6.9

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Table 3: Life expectancy under varying scenarios of COVID-19 attributable mortality in Italy, Germany and Sweden, 2020

Image <th< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></th<>												
Product Italy Control Germany Control Germany Control Sweden Sweden   ge expectancy with actual with actual actual with actual actua		Life expectanc y with COVID-19 accounting 10% of total deaths	81.8	72.0	62.1	52.4	42.7	33.2	24.1	16.0	8.7	4.0
Genary Life Swedan Swe		Life expectancy with COVID-19 accounting 6% of total deaths	82.2	72.3	62.4	52.7	43.0	33.5	24.4	16.2	9.0	4.1
Image <th< th=""><th>Sweden</th><th>Life expectancy with actual number of COVID-19 deaths (5.8%)</th><th>82.2</th><th>72.3</th><th>62.4</th><th>52.7</th><th>43.0</th><th>33.5</th><th>24.4</th><th>16.3</th><th>9.0</th><th>4.2</th></th<>	Sweden	Life expectancy with actual number of COVID-19 deaths (5.8%)	82.2	72.3	62.4	52.7	43.0	33.5	24.4	16.3	9.0	4.2
Image <th< th=""><th></th><th>Life expectancy without COVID-19</th><th>82.7</th><th>72.8</th><th>63.0</th><th>53.2</th><th>43.5</th><th>34.0</th><th>24.9</th><th>16.7</th><th>9.4</th><th>4.4</th></th<>		Life expectancy without COVID-19	82.7	72.8	63.0	53.2	43.5	34.0	24.9	16.7	9.4	4.4
Italy Italy Contrany Cernany   Be Life		Life expectancy with COVID-19 accounting 10% of total deaths	80.5	8.07	6.09	51.1	41.4	32.1	23.5	15.5	9.6	5.6
Pite Italy COVID-19   Perpectancy Elfe Ecounting </th <th></th> <th>Life expectancy with COVID-19 accounting 6% of total deaths</th> <th>80.9</th> <th>2.17</th> <th>61.3</th> <th>51.5</th> <th>41.8</th> <th>32.5</th> <th>23.8</th> <th>15.9</th> <th>9.8</th> <th>2.8</th>		Life expectancy with COVID-19 accounting 6% of total deaths	80.9	2.17	61.3	51.5	41.8	32.5	23.8	15.9	9.8	2.8
Italy <th< th=""><th>Germany</th><th>Life expectancy with actual number of COVID-19 deaths (1.0%)</th><th>81.4</th><th>2.17</th><th>61.8</th><th>22.0</th><th>42.3</th><th>33.0</th><th>24.3</th><th>16.3</th><th>10.2</th><th>6.1</th></th<>	Germany	Life expectancy with actual number of COVID-19 deaths (1.0%)	81.4	2.17	61.8	22.0	42.3	33.0	24.3	16.3	10.2	6.1
Italy <th< th=""><th></th><th>Life expectancy without COVID-19</th><th>81.5</th><th>8.17</th><th>61.9</th><th>52.1</th><th>42.4</th><th>33.1</th><th>24.4</th><th>16.4</th><th>10.3</th><th>2'9</th></th<>		Life expectancy without COVID-19	81.5	8.17	61.9	52.1	42.4	33.1	24.4	16.4	10.3	2'9
Italy Italy   Perform Life Life   Utile expectancy expectancy   with actual expectancy expectancy   expectancy scounting expectancy   expectancy scounting expecancy   expectanc		Life expectancy with COVID-19 accounting 10% of total deaths	82.6	72.8	62.9	53.1	43.3	33.8	24.7	16.5	9.5	4.9
Life Life   Be expectancy   Oup with actual   Without COVID-19   Ge expectancy   Without COVID-19   COVID-19 deaths   P3 83.6   P3 83.6   P3 83.6   P4 73.8   P3 53.5   P3 53.5   P3 53.5   P3 53.5   P4 44.3   P43 34.3   P5 53.5   P6 54.1   P5 53.5   P6 24.3   P6 34.3   P6 25.7   P6 17.3   P6 17.3   P6 17.3   P6 9.7   P6 17.3   P6 9.7   P6 9.7		Life expectancy with COVID-19 accounting 6% of total deaths	82.9	73.2	63.3	53.5	43.7	34.2	25.1	16.8	9.7	5.1
Life Life   Qe expectancy   oup without   vithout without   P9 83.6   P39 54.1   P49 73.8   P39 54.1   P49 44.3   P59 53.9   P60 25.7   P60 25.7   P30 17.3   P60 25.7   P50 17.3	Italy	Life expectancy with actual number of COVID-19 deaths (5.2%)	83.0	73.3	63.4	53.5	43.8	34.3	25.2	16.8	9.7	5.1
- +		Life expectancy without COVID-19	83.6	73.8	63.9	54.1	44.3	34.8	25.7	17.3	10.0	5.3
B 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		Age Group	6-0	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	+06

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## Table 4: Estimates of Years of Potential Life Lost (YPLL) under varying scenarios of COVID-19 attributable deaths in USA, 2020

Age Group	YPLL Without COVID-19	YPLL with COVID- 19 deaths as of 20th July, 2020	COVID-19 deaths accounting 6% death share	COVID-19 deaths accounting 10% death share	Share of YPLL without COVID-19 deaths	Share of YPLL with COVID-19 deaths as of 20th July, 2020
0-1	1597660	839	1042	1726	2.89	0.04
1-4	528026	740	918	1521	0.96	0.03
5-14	404728	1230	1527	2529	0.73	0.05
15-24	2198402	11959	14837	24546	3.98	0.51
25-34	3408302	54773	67930	112235	6.17	2.33
35-44	3730989	116830	144819	238853	6.76	4.96
45-54	6286116	258926	320727	527736	11.38	11.00
55-64	10504149	482421	597013	979343	19.02	20.49
65-74	10931986	596419	737150	1204162	19.80	25.33
75-84	8940175	486643	600244	973948	16.19	20.67
85+	6686000	343636	422028	674976	12.11	14.60
Total	55216531	1549673	2908234	4741575	100.00	100.00
Rate of PYLL	166.8	7.1	8.8	14.3	NA	NA

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	'L)	COVID-19 deaths accounting 10% death share	141	0	963	1444	3309	8974	15872	33263	35046	10055	109067	10.8
veden	ial Life Lost (YF	COVID-19 deaths accounting 6% death share	85	0	581	872	2000	5437	9646	20318	21610	6286	66834	66
S	ears of Potent	COVID- 19 deaths as of 20th July,2020	82	0	564	846	1942	5279	9367	19735	20998	6112	64926	Rate of PVII 1468 79 90 147 1724 15 87 142 1274 64 66 108
taly Germany Sweden	Y	Deaths from all cause Without COVID- 19	16540	14566	37771	42579	69628	136033	234225	337455	297444	100000	1286241	127.4
	(T)	COVID-19 deaths accounting 10% death share	828	1456	5638	12093	32366	106110	211397	326998	394301	97761	1188948	14.2
many	al Life Lost (YP	Age Group Tears of rotatilat Life LOSI (FFLL)   Age Group Deaths COVID-19 <	200413	243724	61092	730129	8.7							
Germany	ears of Potenti	COVID- 19 deaths as of 20th July,2020	82	145	562	1209	3248	10711	21528	33756	41513	10555	123310	1.5
	Y	Deaths from all cause Without COVID- 19	260760	100518	210517	333591	831076	2013960	2534936	3584467	3593104	981000	14443930	172.4
	<u>(П</u>	COVID-19 deaths accounting 10% death share	648	0	1976	6879	25511	68/87	166583	289998	258690	59943	889018	747
ltaly	tial Life Lost (YF	COVID-19 deaths accounting 6% death share	168	0	1 193	4157	15443	47805	101417	177342	1 58893	37036	543679	06
	ears of Poten	COVID- 19 deaths as of 20th July,2020	342	0	1043	3637	13514	41852	88846	155492	139435	32537	476699	62
	۲ ۲	Deaths from all cause Without COVID- 19	133698	59050	115037	173066	487389	967170	1452848	2099375	2555570	830000	8873203	146.8
Italy Germany Swee		Age Group	6-0	10-19	20-29	30-39	40-49	20-29	69-09	70-79	80-89	+06	Total	Bate of PVI I
			-	-	-	-		-					-	-

	DALY			DALY per 100	00 Population	
Age Group	COVID-19 deaths as of 20th July, 2020	COVID-19 deaths accounting 6% death share	COVID-19 deaths accounting 10% death share	COVID-19 deaths as of 20th July,2020	COVID-19 deaths accounting 6% death share	COVID-19 deaths accounting 10% death share
0-1	342	425	708	0.07	0.09	0.14
1-4	303	377	628	0.02	0.03	0.04
5-14	524	652	1086	0.01	0.02	0.03
15-24	5650	7026	11710	0.13	0.16	0.27
25-34	28810	35826	59709	0.61	0.76	1.27
35-44	66453	82633	137722	1.59	1.97	3.29
45-54	161056	200272	333786	3.96	4.93	8.21
55-64	333419	414604	691007	7.90	9.82	16.37
65-74	458616	570286	950477	14.25	17.73	29.54
75-84	416425	517822	863036	25.72	31.99	53.31
85+	324939	404059	673432	48.60	60.43	100.72
Total	1796537	2233981	3723302	5.4	6.7	11.2

Table 6: Estimates of DALY under varying scenarios of COVID-19 in USA, 2020

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Table 7: Estimate of DALY under varying scenarios of COVID-19 in Italy, Germany and Sweden, 2020

											1		1
	hulailoi	COVID-19 deaths accounting 10% death share	0.01	0.00	0.05	0.07	0.19	0.43	1.09	3.67	6.71	10.70	1.09
Y per 1000 Pc		COVID-19 deaths accounting 6% death share	0.00	0.00	0.03	0.04	0.11	0.26	0.65	2.20	4.03	6.42	0.65
		COVID- 19 deaths as of 20th July,2020	0.00	00.00	0.03	0.04	0.11	0.25	0.63	2.14	3.91	6.23	0.64
		COVID-19 deaths accounting 10% death share	54	0	462	768	1921	5816	11588	27432	32834	10492	91367
Sweden		COVID-19 deaths accounting 6% death share	32	0	277	461	1152	3489	6953	16459	19701	6295	435689
	Ţ	COVID- 19 deaths as of 20th July,2020	31	0	269	447	1118	3387	6748	15974	19120	6110	53204
		COVID-19 deaths accounting 10% death share	0.04	0.08	0.29	0.60	1.87	5.18	14.70	36.56	74.92	101.17	11.87
0 Population		COVID-19 deaths accounting 6% death share	0.02	0.05	0.18	0.36	1.12	3.11	8.82	21.93	44.95	60.70	7.12
DALY DAY 100		COVID-19 deaths as of 20th July,2020	0.00	0.01	0.03	0.06	0.18	0.51	1.44	3.59	7.36	9.94	1.17
		COVID-19 deaths accounting 10% death share	319	289	2739	6535	19115	28869	156424	273142	366644	99252	994691
Germany		COVID-19 deaths accounting 6% death share	192	382	1644	3921	11469	41929	93854	163885	219986	59551	596814
		COVID- 19 deaths as of 20th July,2020	31	63	269	642	1878	6867	15371	26841	36029	9753	97745
		COVID-19 deaths accounting 10% death share	0.05	0.00	0.17	0.52	1.63	5.29	16.14	39.44	64.20	72.12	12.01
0 Population		COVID-19 deaths accounting 6% death share	0.03	00.0	0.10	0.31	0.98	3.18	69.6	23.66	38.52	43.27	7.21
DALY per 100		COVID-19 deaths as of 20th July,2020	0.03	00.00	60.0	0.27	0.85	2.77	8.46	20.67	33.65	37.80	6.29
		COVID-19 deaths accounting 10% death share	255	0	1009	3626	14679	50647	120823	237791	237460	59859	726149
ltaly DALY		COVID-19 deaths accounting 6% death share	153	0	605	2176	8807	30388	72494	142675	142476	35915	
		COVID- 19 deaths as of 20th July,2020	134	0	529	1901	7694	26547	63329	124638	124464	31375	380609
		Age Group	6-0	10-19	20-29	30-39	40-49	50-59	69-09	62-02	80-89	+06	Total



Figure 1: Reduction in Life Expectancy at Birth due to COVID-19 attributable deaths in USA, Italy, Germany and Sweden, 2020
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# Role of Interleukin-5 in the Pathophysiology and Treatment of Eosinophilic Asthma

### By Nightingale Syabbalo

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*Abstract*- Asthma is a heterogeneous chronic airway disease with several distinct phenotypes characterized by different immune pathological pathways, clinical features, disease severity, physiology, and response to treatment. Approximately 50% of patients with stable chronic asthma have the eosinophilic phenotype, whereas the remainder have the non-eosinophilic asthma is the most common phenotype in children with acute severe asthma, but neutrophilic asthma is the most common in adult patients presenting with acute severe asthma. T helper 2 (Th2) cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoitein (TSLP), play a very important role in the pathophysiology of eosinophilic asthma. Interlukin-5 is the pivotal cytokine responsible for the proliferation, differentiation, activation, and survival of eosinophils; and promotion of eosinophil migration and airway eosinophilia. Activated eosinophils secrete granular cytotoxic cationic proteins, such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinohil-derived peroxide, and reactive oxygen species.

Keywords: eosinophilic asthma, cytokines, interleukin-5, monoclonal antibodies.

GJMR-F Classification: NLMC Code: WF 140



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# Role of Interleukin-5 in the Pathophysiology and Treatment of Eosinophilic Asthma

Nightingale Syabbalo

Abstract- Asthma is a heterogeneous chronic airway disease with several distinct phenotypes characterized by different immune pathological pathways, clinical features, disease severity, physiology, and response to treatment. Approximately 50% of patients with stable chronic asthma have the eosinophilic phenotype, whereas the remainder have the noneosinophilic asthma. Eosinophilic asthma is the most common phenotype in children with acute severe asthma, but neutrophilic asthma is the most common in adult patients presenting with acute severe asthma. T helper 2 (Th2) cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoitein (TSLP), play a very important role in the pathophysiology of eosinophilic asthma. Interlukin-5 is the pivotal cytokine responsible for the proliferation, differentiation, activation, and survival of eosinophils; and promotion of eosinophil migration and airway eosinophilia. Activated eosinophils secrete granular cytotoxic cationic proteins, such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinohilderived peroxide, and reactive oxygen species. The cytotoxic cationic proteins lead to epithelial injury, inflammation and airway remodeling. Additionally, eosinophils can synthesize and secrete a plethora of pro-inflammatory mediators, such as lipid-derived mediators, cytokines, chemokines, and growth factors, which orchestrate eosinophilic airway inflammation, and airway hyper responsiveness. IL-5 is of paramount importance in eosinophil immunopathological effects. Pharmacologic blockade of IL-5 or its receptor ( $\alpha$ ) has yielded the discovery of biologics, such as mepolizumab, reslizumab, and benralimab, which are useful for the treatment of coticosteroid-resistant eosinophilic asthma.

*Keywords:* eosinophilic asthma, cytokines, interleukin-5, monoclonal antibodies.

#### I. INTRODUCTION

sthma is a significant public health problem, affecting more than 358 million individuals globally,<sup>1</sup> and its prevalence has been increasing during the last 40 years.<sup>1-3</sup> It is the most common chronic respiratory disease in children in developed countries,<sup>4</sup> and its prevalence is steadily increasing in the developing world.<sup>5</sup>

Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterized by different immunopathological pathways, clinical presentation, severity of the disease, and response to treatment.<sup>6-11</sup> There are several clinical, molecular, and immunogenetic phenotypes of asthma,<sup>12,13</sup> but the

Author: MB., ChB., PhD., FCCP., FRS Professor of Physiology and Medicine Copperbelt University M. C. Sata School of Medicine Kitwe Zambia. e-mail: nightsyab@gmail.com phenotypes of asthma can be simply classified into four phenotypes using induced sputum cytometry.<sup>7,14</sup> The phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma.<sup>7</sup>

Eosinophilic asthma has elevated sputum eosinophil count  $\geq 3\%$ ,<sup>7,14-16</sup> whereas neutrophilic asthma has elevated sputum neutrophil count between  $\geq 61\%$ ,<sup>15</sup> and  $\geq 64\%$ ,<sup>16</sup> depending on the study. Mixed granulocytic phenotype is characterized by increase in both sputum eosinophils (>3%), and neutrophils (>61% or >64%).<sup>15</sup> Paucigranuocytic phenotype includes patients with very few eosinophils (<3%), and neutrophils (<61% or <64%) in induced sputum.<sup>7,15,17</sup> Non-eosinophilic asthma is the term used to classify patients with low eosinophil numbers (<3%), which include neutrophilic asthma, and paucigranulocytic phenotype.<sup>7</sup>

Eosinophilic airway inflammation play a key role in the pathophysiology of eosinophilic asthma. Activated eosinophils secrete granular cytotoxic cationic proteins, such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil-derived peroxide, and reactive oxygen species. The cytotoxic cationic proteins lead to epithelial injury, inflammation and airway remodeling. Additionally, eosinophils can synthesize and secrete a plethora of inflammatory mediators, such as leukotrienes, prostaglandins, cytokines, chemokines, and growth factors, which orchestrate eosinophilic airway inflammation, and airway hyper responsiveness (AHR).

Eosinophilic asthma is regarded at T helper 2 (Th2)-driven phenotype. Th2 cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoitein (TSLP), play a very important role in the pathophysiology of eosinophilic asthma. Interlukin-5 plays a pivotal role in the proliferation, differentiation, migration, activation, and survival of eosinophils. Together with IL-4, IL-13, IL-25, IL-33, and TLP, it is responsible for airway eosinophilic inflammation, sub epithelial basement membrane fibrosis, extracellular matrix protein deposition, and airway smooth muscle (ASM) cell hyperplasia and hypertrophy.

Most patients with stable eosinophilic asthma are responsive to the step-wise guideline therapies, including high dose inhaled corticosteroids (ICS), long-acting  $\beta$ -2 agonists (LABA), and leukotriene receptor antagonist (LTRA).<sup>1,18,19</sup> However, there is a sub-group of

severe asthma patients with increased airway allergic inflammation despite treatment with high-dose ICS or oral corticosteroids (OCS), and their inflammatory biomarkers remain high even after corticosteroid injections.<sup>20</sup> This sub-group of patients with eosinophilic and steroid-resistant asthma require alternative targeted therapies such as interleukin antagonists (ILA), and bronchial thermoplasty.

#### II. Eosinophils

Eosinophils play a pivotal role in the pathogenesis and severity of asthma, and other allergic diseases such as allergic rhinitis, atopic eczema,<sup>21</sup> and eosinophilic granulomatosis with polyangiitis.<sup>22</sup> The eosinophil was first described by Paul Ehrlich in 1879, after he developed the fruorescent dye eosin which coloured basic protein bright red.<sup>23</sup> Hematologic ally, it was identified as eosinophil in an autopsy of a 48-yearold male patient who died of status asthmaticus by Dr. Fraenkel in 1900.24 In 1953, Houston, et al.25 demonstrated that patients dying from status asthmaticus had airway mucosa infiltration by activated eosinophils. Thereafter, Bousquet and colleagues,<sup>26</sup> reported that patient with chronic asthma had an increase in eosinophils in peripheral blood. bronchoalveolar lavage (BAL) fluid, and lung biopsy specimens.

Eosinophils are polymorphonuclear cells, with a diameter of about 10-16  $\mu$ m, and constitutes 1-4% of circulating white blood cells. They have a nucleus usually with two lobes, and have large cytoplasmic granules that stain beautifully deeply red after staining with eosin, using the Romanowsky method.<sup>27</sup> They have a very short life span of about 1-6 hr in the circulation, but can live longer in allergic inflamed tissues, such as lungs and airways.

Eosinophils and other leukocytes are formed from bone marrow CFU-GM progenitor cells during myelopoiesis.<sup>28</sup> The pluripotent myeloid progenitor cells give rise to CD34+ IL-5R $\alpha$  eosinophil progenitor cells, which by the actions of haematopoietic factors, growth factors, and cytokines lead to eosinophils maturation.<sup>28,29</sup> The differentiation of eosinophils is regulated by transcription factors GATA-binding protein 1 (GATA-1), PU.1, and the CCAAT-enhancing binding protein (c/EBP) family.<sup>30</sup> GATA-1 seems to have the most important role, because disruption of GATA1 gene in mice results in a strain completely without eosinonophils.<sup>29</sup> Interleukin-4 is essential, because of its requirement to the Th2 cell commitment, and activation via stimulation of key transcription factors, such as GATA3 and STAT6.31 Interleukin-5, IL-3, and GM-CSF synergistically contribute to the development of mature eosinophils, and other leucocytes, through induction of bcl-xl expression.<sup>29</sup> Interleukin-5 is the most specific and central cytokine in eosinophils, and basophils biology. It plays a key role in eosinophilic proliferation, differentiation, and the release of eosinophils from the bone marrow into the blood stream, acting synergistically with eotaxin-1, -2, and -3.<sup>31</sup> Eotaxin-1 (CCL11) is a specific chemo attractant of eosinophils and stimulates migration of CD34+ progenitor cells, and release of eosinophils into the peripheral blood, and accumulation in the lungs.<sup>32,33</sup> Eotaxin-1 and its receptor CCR3, may be involved in the survival and other immunological functions of eosinophils.<sup>31</sup>

Migration of eosinophils from the vasculature into lung tisssue is facilitated by eosinophils-specific adhesion molecules, such as  $\beta$ 1 intergrin very late antigen (VLA-4), the vascular cell adhesion molecule (VCAM-1), and the P-selectin glycoprotein ligand (PSGL-1).<sup>34</sup> VLA-4 is an integrin which is expressed on the membrane of eosinophils after stimulation by eotaxin-1. It ligands with the VCAM-1 integrin expressed on the vascular membrane, resulting in the activation and firm adhesion to eosinophils. Thus, facilitating eosinophil diapedesis through the endothelium into lung tissues.<sup>34</sup>

Recruitment and migration of eosinophils into the airway mucosa is mediated by coordinated action of cytokines, such as IL-5, IL-4, and IL-13, and chemokines, eotaxins-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26), RANTES, and MCP1/4.<sup>34-36</sup> In particular, eotaxin-1 and its receptor CCR3, play an important role in driving eosinophils into allergic inflamed tissues in the airways. Leukotriene C4 (LTC4) is one of the most potent eosinophil chemo attractact, and is also involved in eosinophil recruitment and cascade. Table 3 summarizes the physiological functions of IL-5 in eosinophil immunobiology.

Eosinophils exhibit chemotaxis, and diapedesis, but they are weak phagocytes. They appear to be used combating selectively for helminth parasitic infections,<sup>37,38</sup> such as Stronavloides stercolis: Schistosoma haematobium and S. mansoni; Taenia saginata; and Diphyllobothrium latum. However, they also play an important immunological role in viral infections, especially respiratory viral infections.<sup>39</sup>

#### III. Eosinophil Surface Receptors

Eosinophils possess a wide repertoire of surface adhesion molecules and receptors, for cytokines, chemokines, and growth factor receptors, lipid mediators receptors, chemo attractant receptors, adhesion receptors, Toll-like receptors, and FcɛR1 receptors.<sup>40-44</sup> Eosinophilic signaling and inflammatory activity is regulated via cytokines, chemokines, leukotrienes and prostaglandins secreted by Th2 cells, ILC2s, mast cells, and basophils through their respective receptors on the surface of eosinophils.

Eosinophils express the FcER1 receptor for immunoglobulins (Ig), IgE, IgG, IgA, IgM, and IgD, which serves a key role in allergic inflammatory responses.

During allergen exposure, the high-affinity Fc $\epsilon$ R1 tetramer ( $\alpha\beta\gamma\gamma$ ) receptor on the surface of eosinophils interact with the Fc portion of the IgE molecule leading to activation and degranulation of eosinophils, and release of cationic proteins and other mediators.<sup>44</sup> The most important cytokine receptor on the surface of eosinophils is the heterodimer IL-5 receptor, which plays a key role in eosinophil immunopathology.<sup>44,45</sup> Eosinophils also express other cytokine receptors, including IL-4, IL-13, IL-17, IL-25, IL-33, and TSLP, and growth factor receptors, such as transforming growth factor- $\beta$ . The above cytokines play a synergistic role in the pathophysiology of eosinophilic asthma.

#### IV. Eosinophil Mediators

Activated eosinophils either by allergic and nonallergic pathways, undergo autolysis and release an array of eosinophil-specific granules found in the extracellular DNA traps.<sup>46</sup> The most predominant bioactive mediators released from the granules are the four cytotoxic cationic proteins, such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophilderived neurotoxin (EDN), eosinophil-derived peroxide (EDPX), and reactive oxygen species.44,44,47,48 Major basic protein, ECP, and EDPX are toxic to a number of cells, including airway epithelial cells,<sup>49</sup> and ASM cells, and contribute to airway hyper responsiveness (AHR).<sup>50</sup> Eosinophil-derived neurotoxin, and ECP belong to the RNAase A family of granule proteins that have ribonuclease activity.51 They are associated with host defense against viruses, and may play a role in tissue remodeling.<sup>51</sup> Eosinophil-derived neurotoxin is toxic to nerves,<sup>52</sup> whereas eosinophil peroxidase produce reactive oxygen species, and reactive nitrogen intermediates, which promote oxidative stress in tissue, causing cell death by apoptosis and necrosis.<sup>49</sup>

Eosinophils can synthesize and release a plethora of inflammatory mediators, including lipidderived mediators, such as histamine, cysteinyl leukotrienes, prostaglandins, thromboxanes, and PAF; cytokines, chemokine, enzymes, and growth factors.53,54 Leukotrienes and prostaglandins promote airway smooth muscle contraction, mucus secretion, vasodilatation and edema formation, which lead to airway obstruction.54 They also activate mast cells and basophils through their receptors to secrete more histamine, prostaglandins, and leukotienes, thus amplifying the eosinophilic inflammatory responses.<sup>55</sup>

Additionally, eosinophils synthesize and secrete several Th2 and ILC2 cytokines, such as IL-3, IL-4, IL-5, IL-9, IL-13, IL-15, IL-23, IL-25, IL-33, GM-CSF, TNF- $\alpha$ , and GM-CSF. Interleukin-5, IL-13, and GM-CSF secreted by eosinophils promote eosinophilic function and survival in an autocrine fashion.<sup>53</sup> Interleukin-13, and IL-25 are pro-fibrotic cytokines which lead to subepithelial basement membrane fibrosis, deposition

of extracellular matric proteins, airway remodeling, and fixed airflow limitation. Th2 cytokines, such as IL-5, IL-4, IL-13, IL-25, IL-33, and TSLP are responsible for airway eosinophilia, AHR, and remodeling. They promote airway smooth muscle (ASM) cell proliferation and hypertrophy, amplify ASM cell contraction, and lead to sub mucous glands and goblet cell hyperplasia and mucus hyper secretion. Eosinophils also secrete growth factors, such as TGF- $\beta$ , VEGF, IL-13, and enzymes, including MMP-9, and TIMP-1 which are responsible for the development of ASM hypertrophy and sub epithelial fibrosis, hence, severe fixed airflow obstruction,<sup>57</sup> and corticosteroid resistance. Table 1 shows the list of pro-inflammatory mediators synthesized and secreted by activated eosinophils.

#### V. Cytokines

Pro-inflammatory cytokines play a central role in the pathophysiology of allergic diseases, such as eosinophilic asthma.<sup>58</sup> The cytokines implicated in the pathophysiology of eosinophilic asthma are derived mainly from Th cells.<sup>58</sup> The other sources of cytokines include, mast cells, basophils, eosinophils,<sup>45,59,60</sup> dendritic cells, natural killer cells, and NK T cells.<sup>61-64</sup> Novel T cells, such as ILC2, Th9, Th17, Th22 cells, Treg cells, and nuocytes,<sup>64,65</sup> and structural cells including epithelial cells, fibroblasts and airway smooth muscle cells can also produce cytokines and chemokines.<sup>61</sup>

Notably, there is cross-talk between eosinophils and mast cells, and the cytokines and chemokines networks in orchestration the allergic inflammatory responses.<sup>60,66</sup> Each of these cells produce an array of cytokines and chemokines which promote secretion of more cytokines by the other inflammatory cells, thus establishing paracrine and even autocrine positive feedback loops.

Th2 lymphocyte, ILC2s, mast cell, and eosinophil cytokines possess overlapping biological activities; they can synergize or antagonize the effects of other cytokines. For example, IL-5, II-4, IL-13, IL-25, and IL-33 are the key drivers of the inflammatory process in eosinophilic asthma; and IL-4 and IL-13 are central Th2 cytokines with distinct overlapping roles, particularly in remodeling and airwav bronchial hyperresponsiveness.<sup>58</sup> Similarly, interferon-y, a Th1 cytokine acts in conjunction with Th2 cytokines (IL-3, IL-4, and IL-5) in maintaining chronic airway inflammation in patients with asthma. The most important cytokines in the pathophysiology of eosinophilic asthma include IL-5, IL-4 IL-13, IL-25, IL-33, and TSLP. IL-5 is the regarded as the master minder cytokine.

#### VI. INTERLEUKIN-5

Interleukin-5 is mainly produced and secreted by Th2 lymphocyte and group 2 innate lympoid cells (ILC2).<sup>67-71</sup> Th2 cells, and ILC2 secrete IL-5 after been activated by dendritic cells in response to allergens, and inflammatory mediators.<sup>72</sup> Interleukin-4 is essential for the promotion of Th2 cell differentiation from naive T helper cells (Th0), and activation of Th2 cells leading to the production and release of cytokines, such as IL-4, IL-5, IL-13, IL-25, IL-33, and TSLP.<sup>62</sup> The differentiation of Th2 cells is transcribed by GATA-3 acting as a master signaling factor,<sup>62,73</sup> and STAT6 serving as a key transcription factor.<sup>73</sup> IL-5 secretion from ILC2 is also dependent on GATA-3 activation induced by epithelilal "alarmin" cytokines, such as IL-25, IL-33, and TSLP.<sup>73</sup>

Interleukin-5 is a cytokine composed of 134amino acid proteins that form a 52-kDa homodimer.74-76 It belongs to the haematopoietic growth factor cytokine family, which also include IL-3 and GM-CSF.<sup>74</sup> It is highly specific for eosinophil formation,<sup>77</sup> by stimulating the proliferation, and differentiation production. of eosinophils from myeloid progenitor cells in the bone marrow.<sup>78,79</sup> IL-5 also aids in the extrusion of eosinophils from the marrow. Peripherally, IL-5 participates in the terminal maturation of the eosinophil in the circulation. Interleukin-5 is important in the recruitment and activation of eosinophils in the lungs, and for eosinophil survival by preventing apoptosis. It plays a critical role in diapedesis of eosinophils by facilitating endothelial adhesion, and promotes chemotaxis in inflamed lung tissues.<sup>80</sup>

The interleukin-5 receptor is a heterodimer composed of a specific subunit, IL-5R $\alpha$ , and a separate motif for binding to the signaling subunit,  $\beta$ c, of the receptor.<sup>76,79</sup> The IL-5R $\alpha$  is specific to IL-5 binding, whereas the  $\beta$ c chain also binds to IL-3, and GM-CSF.<sup>76,79</sup> The IL-5R $\alpha$  subunit is expressed about threefold on eosinophils compared with basophils.<sup>80,81</sup>

Binding of IL-5 to the IL-5 receptor triggers activation of a complex intracellular signaling involving JAK1/2 and STAT1/3/5 modules, p38 and ERK MAP kinases, and NF-k $\beta$  transcription factor.<sup>82</sup> JAK2, and Lyn and Raf-1 are involved in eosinophil survival by preventing apoptosis, and Raf-1 is specifically involved stimulating eosinophil activation in and degranulation.82,83 Another IL-5 signaling pathway include activation of intracellular kinases, such as phosphoinositide 3-kinase (PI3K), and mitogenactivated ptotein kinases (MAPK).83,84 Through NFdependent mechanism, p38 MAPK up-regulates eosinophil recruitment into allergic airways, and activates synthesis of pro-inflammatory mediators, including cytokines, chemokines, and leukotrienes, and prostaglandins.<sup>85,86</sup> These mediators orchestrates airway eosinophilic inflammation, subepethelial reticular membrane fibrosis, submucous gland hyperplasia and mucus secretion, and ASM cell proliferation, hyperplasia and hypertrophy.

InterleukinL-5 and its receptors (IL-5R $\alpha$ , CD125) expressed on the surface of eosinophils, basophils, and a subset of mast cells cells are the central players

responsible for airway eosinophilia. Therefore, targeting IL-5 or its receptor subunit IL-5R $\alpha$  is a logical approach for add-on treatment of severe difficult-to-treat eosinophilic asthma, and corticosteroid-resistant asthma phenotypes.<sup>87-89</sup> There are currently two marketed IL-5 monoclonal antibodies (mAb) targeted against IL-5 (mepolizumab, and reslizumab), and one IL-5Rα mAb targeted against (benralizumab). Interleukin-5 antagonists bind to distinct epitopes of IL-5 interfering its binding to IL-5 receptors expressed on the surface of eosinophils. Anti-IL-5R antibodies also induce targeted-cell lysis and have been shown to reduce circulating eosinophil counts rapidly.

#### VII. Mepolizumab

Mepolizumab (Nucala ®) is an *N*-glycosylated lgG1/k humanized monoclonal antibody formed by two light chains and two heavy chains bound by a disulphide bond, with a molecular weight of 149.2 kDa.<sup>90</sup> Mepolizumab binds to the  $\alpha$ -chain of IL-5 with both specificity (IC50 <1nm), and affinity (*K*d = 4.2 pM),<sup>90</sup> with a dissociation constant of 100 pM, thus preventing it from binding to the  $\alpha$  subunit of the IL-5 receptor expressed on the surface of the eosinophil.<sup>90-92</sup> This results in inhibition of IL-5 signaling and bioactivity which lead to reduction in the production, differentiation, activation and survival of eosinophils. Mepolizumab inhibit eosinophilic activation and the release of myriad of inflammatory mediators from the eosinophils, thus preventing airway eosinophilic inflammation.<sup>92-94</sup>

Mepolizumab (SB-240563, GlaxoSmithKline) was the first biological anti-IL-5 agent to be tested in randomized clinical trials (RCT) in 2000.<sup>95</sup> The first clinical trial of mepolizumab in patients with asthma showed a reduction in sputum and blood eosinophil count but no change in bronchial hyper responsiveness, and no effect on the late asthmatic response.<sup>95</sup> In the phase 2b/3 DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma) much larger population trial, Pavord et al.<sup>96</sup> confirmed that mepolizumab reduced sputum and blood eosinophil counts, and also significantly reduced asthma exacerbation rates. Additionally, mepolizumab improved the asthma control questionnaire (ACQ) scores, and the asthma quality of life questionnaire (AQLQ) scores.<sup>96</sup>

In the MENSA (MEpolizumab as adjunctive therapy iN patients with Severe Asthma) study, Ortega and colleagues,<sup>97</sup> showed that treatment with intravenous (IV) or subcutaneous (SC) mepolizumab decreased the rate of exacerbations by 47% and 53% respectively. It also reduced exacerbations requiring emergency room visits or hospitalization by 32% for IV and 61% for SC mepolizumab. In addition, patients in both IV and SC mepolizumab groups showed significant improvement in the quality of life, and asthma control as assessed by the St. George's Respiratory Questionnaire (SGRQ), and the ACQ-5, and a slight improvement in FEV1.<sup>97</sup>

The SIRUS (Sterold Reduction with mepoliz Umab Study) in patients with severe asthma and peripheral blood eosinophilia while on maintenance corticosteroid revealed that, patients on mepolizumab had a likelihood of reducing corticosteroid-dose 2.37 times greater than patients on placebo.98 Patients on mepolizumab were also to reduce the corticosteroid dose by 50%, and had lower exacerbation rates, and improved asthma control despite receiving lower doses of ICS or OCS, thus demonstrating a steroid-sparing effect.98 Recently, Chupp et al.99 have confirmed a significant change in the St. George's Respiratory Questionnaire score at the 24<sup>th</sup> week of treatment with add-on mepolizumab. Patients receiving mepolizumab showed improvement in symptoms, and health-related guality of life (HRQoL) scores, compared with control subjects receiving placebo. In summary, mepolizumab has a very good safety and tolerability profile. Add-on treatment with mepolizumab has been shown to improve the ACQ scores, AQLQ scores, SGRQ scores, and FEV1. Additionally, add-on mepolizumab has been shown to reduce the rate of exacerbations, and the dosage of corticosteroid or use of other drug modifiers.96-99

Mepolizumab was approved by the FDA on March 23, 2015 for add-on treatment of eosinophilic asthma in adults and children aged  $\geq 12$  years.<sup>100</sup> Meplizumab was also approved by the European Medicines Agency Committee for Medicinal Products for human use in December 2015.101 Nucala is also indicated for the treatment of eosinophilic granulomatosis with polyangitis (EPGA/Churg/Strauss Syndrome). Mepolizumab is not indicated for treatment of the relief of acute bronchoconstriction and status asthmaticus or any other eosinophilic syndromes.

The recommended dose is 100 ma administered subcutaneously every 4 weeks, and it is well tolerated and has been found to be safe.<sup>100</sup> The most common adverse effects with Nucala include injection site reaction, headache, backache, fatigue, weakness, nasopharyngitis, and muscle upper respiratory tract infection. Acute and delayed systemic reactions, including anaphylaxis, urticarial rash, angioedema, bronchospasm, and hypotension may occur. Anaphylaxis is rare (<1%), but patients need to be monitored after treatment for these adverse effects.

Eosinophils play an important role in protection against parasitic infection, including helminth infestation. Patients with pre-existing helminth infections should be treated for the infection before mepolizumab therapy. If individuals become infected whilst receiving treatment with Nucala and do not respond to anti-helminth treatment, temporary discontinuation of mepolizumab should be considered.

#### VIII. Reslizumab

Reslizumab (Cingair®), previously known as SCH55700 (Scherig-Plough), is a fully humanized, IgG4/k monoclonal antibody with high affinity for IL-5. The monoclonal antibody has an ERRR configuration (glutamine, arginine, arginine, arginine) corresponding to amino acids 89-92 on the IL-5 antibody molecule. This region is critical for its interaction with the IL-5 receptor which results into inhibition of its bioactivity.<sup>102</sup>

Several randomized clinical trials (RCT) have been conducted on the safety and efficacy of reslizumab. Kips et al.<sup>103</sup> in the first phase 2 pilot study, in patients with severe persistent asthma showed that reslizumab lowered sputum and eosinophil levels, and induced a transient increase in FEV1. A larger phase 2 trial, conducted by Castro el al.<sup>104</sup> showed that treatment with reslizumab significantly increased FEV1, and improved symptoms control, especially in patients with very high eosinophilia and concomitant nasal polyps. Two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials by Castro et al.105 demonstrated that reslizumab decreased the annual rate of asthma exacerbation by 50-59% in severe asthmatics with blood eosinophil count >400 cells/ml. Reslizumab also improve asthma symptom control and slightly improved FEV1.<sup>105</sup>

Bjermer and colleagues,<sup>106</sup> in phase 3 trial, have shown that therapy with reslizumab resulted in significant increase in pulmonary function (FEV1), including airflow limitation in peripheral airways, i.e., increase in forced expiratory flow at 25-75% of forced vital capacity (FEF25-75%). Treatment also improved self-reported asthma control, and quality of life. Brusselle and colleagues have also reported that reslizumab is able to reduce asthma exacerbations, and improve lung function in patients with late-onset eosinophilic asthma.<sup>107</sup>

Reslizumab was approved on March 23, 2016 by the FDA for patients aged  $\geq 18$  years as add-on maintenance therapy for severe uncontrolled eosinophilic asthma.<sup>108</sup> The approved dosage for reslizumab is 3 mg/kg intravenously infused over 20-50 minutes every 4 weeks. It is safe and well tolerated by the patients. The most common side effects of Cingair include headache, nasopharyngitis, myalgia, and fatigue. Anaphylaxis occurs in about 0.3% of the patients,<sup>109</sup> and the U.S. Food and Drug Administration recommends that patients should be observed in a setting where health care professionals are available to treat the adverse reactions. If the patient experiences a severe reaction including anaphylaxis, reslizumab infusion should be discontinued immediately, and the patient should be treated for the adverse event.

Eosinophils play an important in combating helminth infections. Treat patients with pre-existing helminth infections before initiating Cinqair. If patients become infected while receiving treatment with reslizumab and do not respond to anti-helminth treatment, discontinue treatment with reslizumab until parasitosis resolves.

#### IX. Benralizumab

Benralizumab (Fasenra®), formerly called MEDI-563 (AstraZeneca-MedImmune) is a humanized afucosylated IgG1/k monoclonal antibody, developed via hybridoma technology, which selectively recognize the isoleucin-61 residue of domain 1 of human IL-5R $\alpha$ , located near IL-5 binding site.110,111 As a result, the interaction of benralizumab with its recognition site on IL-5Ra block IL-5 binding to target cells, thus preventing hetero-dimerization of IL5R $\alpha$  and  $\beta$ c subunit, and the subsequent activation of IL-5-dependent signaling pathway.<sup>112</sup> Through the constant Fc region, benralizumab bind to the  $FcyRIII\alpha$  membrane receptor expressed by natural killer cells, which upon activation release the pro-opoptotic proteins granzyme D and perforin, which are responsible for eosinophil apoptosis implemented via antibody-dependent cell-mediated cytotoxicity.<sup>113-115</sup> All these effects cause a reduction in eosinophil numbers in the airway mucosa, submucosa, sputum, blood, and bone marrow.<sup>116</sup>

Preliminary RCT have shown that treatment with benralizumab results in a decrease in blood eosinophil count to almost depletion, which is associated with reductions in the rate of exacerbations, and improvement in the ACQ-5 scores.117, 118 The SIROCCO RCT showed that treatment with benralizumab significantly reduced exacerbation rates, and improved lung function, and asthma control in patients with severe asthma uncontrolled on high-dose inhaled corticosteroids and long-acting *β*-agonists.<sup>119</sup> FitzGerald and colleagues in the CALIMA study showed that treatment with subcutaneous benralizumab 30 mg every 4 weeks resulted in a 36% reduction in exacerbations, and a significant increase of 125 ml in FEV1.<sup>120, 121</sup>

The ZONDA phase III oral corticosteroid-sparing trial, demonstrated that add-on benralizumab treatment resulted in up to 51% reduction in annual asthma exacerbation rates versus placebo. There was also a significant improvement in lung function as measured by FEV1. The FEV1 increased by 159 ml, and the improvement in lung function was seen as early as 4 weeks after the initiation of the treatment.<sup>122</sup> Additionally, there was a 75% median reduction in daily oral corticosteroid (OCS) use, and discontinuation of OCS in 52% of the eligible patients.<sup>122</sup> Noteworthy, the BORA RTC revealed that long-term use of add-on benralizumab was associated with a very good safety and tolerability profile.<sup>123</sup> In real-life daily clinical practice, the therapeutic effects of Fasenra may even be better than what is observed in randomized, double-blind clinical trials.124

Benralizumab was approved by the U.S. Food and Drug Administration on November 14, 2017, as add-on therapy for people with severe eosinophilic asthma aged 12 years and older, and those whose asthma is not controlled with current asthma medication.<sup>124</sup> Benralizumab has a half-life of 15-18 days, and is available as a single-dose pre-filled syringe. The recommended dose is 30 mg/ml injection subcutaneously every 4 weeks for the first three doses, thereafter every eight weeks. The most common adverse effects of Fasenra include headache (8.6%), nasopharyngitis (4%), arthralgia (3.9%, cough (3.3%), injection site reaction (2.2%), urticaria rash. Other rare adverse events include chills, nausea, dysgeusia, tremor. dizziness hot flushes. asthenia. and hyperhidrosis.

It is not known if Benralizumab will influence helmith infestation or response to anti-helminth treatment. The manufacturers recommend treatment of the parasitosis before initiating Fasenra, and if patients become infected while receiving Fasenra and do not respond to anti-parasitic agents, to discontinue benralizumab until the infection resolves.

#### X. Criteria for Initiation of Interleukin-5 Antagonists

Biologics should be recommended early in the management of established eosinonophilic asthma diagnosed using pharmacodynamic biomarkers, such as sputum and blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum perisostin, dipeptidyl peptidase-4, and osteopontin.<sup>126-130</sup> Long-term treatment with biologics, such as omalizumab (anti-IgE),<sup>131,132</sup> and mepolizumab,<sup>132</sup> significantly reduce airway wall and reticular membrane thickening. Phipps et al.<sup>133</sup> have reported that mepolizumab is associated with significant reductions in tenascin and lumican deposition in the reticular basement membrane in human atopic skin.<sup>133</sup> If mepolizumab and other anti-IL-5 antagonists exhibit similar effects in eosinophilic airways inflammation, they may be capable of preventing subepithelial fibrosis, and progressive decline in lung function in patients with eosinophilic asthma.

The GINA guidelines,<sup>1</sup> and NAEPP<sup>19</sup> yardsticks for step-up treatment for severe refractory asthma, recommend initiation of biologics, such as anti-IgE, and anti-interleukin (IL)-5 monoclonal antibodies for patients with eosinophilic asthma at step 5. The latest ERS/ATS Task Force guidelines,<sup>134</sup> recommend using anti-IL-5 and anti-IL-5 receptor  $\alpha$  for severe uncontrolled adult eosinophilic asthma phenotypes, using a blood eosinophil cut-point of 150 cells, $\mu$ L<sup>-1</sup> to guide anti-IL-5 initiation in adult patients with severe asthma. The guidelines also suggest specific eosinophil  $\geq$  260 cells, $\mu$ L<sup>-1</sup>, and FeNO 19.5 ppb cut-offs to identify adolescents or adults with the greatest likelihood of

response to anti-IgE therapy. Table 3 shows the three anti-II-5 antagonists and their weekly costs.

few There are reports on the pharmacoeconomical aspects of the newly introduced biologics for the treatment of severe steroid-resistant eosinophilic asthma. Bogart et al.<sup>135</sup> using a hypothetical model estimates that mepolizumab without bronchial thermoplasty (BT) was the most cost-effective option for biological responders, with a 10-year-per-patient cost of US\$116,776. In patients who do not respond to eosinophilic targeted biologics, bronchial thermoplasty is more cost-effective option. Similarly, an indirect comparison of BT with omalizumab in patients with moderate-to-severe allergic asthma in the USA reported greater than 60% chance that bronchial thermoplasty was cost-effective relative to omalizumab and standard therapy at the willingness-to-pay of \$100,000 per qualityadjusted life years (QALY).<sup>136</sup> However, bronchial thermoplasty is a complex sophisticated procedure which requires critical selection of the patients. experienced pulmonologist, and anesthetists, excellent bronchoscopic skills, and dedicated intense postprocedural management and follow-up.<sup>137-140</sup>

#### XI. CONCLUSION

Eosinophilic asthma is a well characterized phenotype of asthma, which is driven by Th2 cytokines, such as IL-4, IL-4, IL-13, IL-25, IL-33, and TSPL. Interlekin-5 plays a central role in the differentiation, proliferation, maturation, survival, and activation of eosinophils. Activated eosinophils secrete cytotoxic cationic proteins, radical oxygen species, cytokines, chemokines, and growth factors which are responsible for epithelial injury, airway inflammation, AHR, and airway remodeling. Targeting IL-5 and its receptor with biologics, such as mepolizumab, reslizumab, and benralizumab is a novel therapeutic strategy for the treatment of severe refractory, steroid unresponsive eosinophilic asthma. Early use of anti-IL-5 antagonists may prevent the progressive decline in lung function. and improve the quality of daily living.

#### Conflicts of interest

The author reports no conflicts of interest in this manuscript.

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Table 1: Pro-inflammatory mediators synthesized and secreted by eosinophils

Major basic protein (MBP)		
Eosinophil cationic protein (ECP)		
Eosinophil-derived neurotoxin (EDN)		
Eosinophil-derived peroxide (EDPX)		
Reactive oxygen species: superoxide, peroxide, and hypobromite		
Prostaglandins: PGD2		
Cysteinyl leukotrienes: LTC4, LTD4, LTE4		
Throboxane B2: TXB2		
Platelet activating factor (PAF)		
Cytokines: IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-23, IL-25, IL-33, and TNF-α,		
GM-CSF		
Chemokines: eotaxin-1, -2, and -3, RANTES, P-selectin, MIP-1, MCP-3,		
MCP-4		
Enzymes: histaminases, arylsulfatase, MMP-9, TIMP-1		
Growth factors: TGF-β, VEGF, PDGF		
Abbreviations: LT, leukotriene; IL, interleukin; MMP, matrix metalloproteinases; TIMP, tissue inhitors of metalloproteinases; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; GM-CSF, granulocyte macrophage colony-stimulating factor; TGF- $\beta$ , transforming growth factor- $\beta$ ; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor.		

Table 2: Physiological functions of IL-5 in eosinophil immunobiology

Stimulation of proliferation, and differentiation of IL-5Ra-expressing eosinophil committed progenitor cells

Stimulation of maturation of eosinophils

Facilitation of exit of eosinophils from bone marrow

Promotion of eosinophil navigation and migration in the circulation

Aids eotaxins, and adhesion molecules in diapedesis of eosinophils through the endothelial cells

Facilitation of migration of eosinophils to inflamed lung tissues and airways

Activation of eosinophils, and release of pro-inflammatory mediators

Prolongs eosinophil survival synergistically with other anti-apoptotic cytokines

# Table 3: Approved interleukin-5 and IL-5Ra antagonists for eosinophilic asthma IL-5 antagonist Mepolizumab Reslizumab Benralizumab

Date of approval	Nov 4, 2015	March 23, 2016	Nov 14,2017
Mechanism of action	IL-5 antagonist	IL-5 antagonist	t IL-5Rα blocker
Route of Administratio	n Subcutaneous	Intravenous	Subcutaneous
Route/frequency	100 mg/4 wk	3mg/kg/4 wk	30 mg/4 wk
Injection	100 mg powder	100 mg/10 mL	30 mg/1 mL
Eosinophil cut-point	$\geq$ 150 cells/ $\mu$ L	$\geq$ 400 cells/ $\mu$ L	≥150cells/µL
FeNO cut-offs	≥19.5 ppb	≥19.5 ppb	≥ ppb
Cost/injection	\$2,868	\$2,580	\$4,752

FDA-approved interleukin-5, and IL-5Rα antagonists, and the cost of treatment. Adapted from The Medical Letter on Drugs on Therapeutics 2018; 60:33; and the European Respiratory Society/American Thoracic Journal Task Force. European Respiratory Journal 2020; 55(1):1900588.



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## Accuracy of Barrett Versus Third Generation Intraocular Lens Formula Across all Axial Lengths in Indian Eyes

By Dr. Tamilarasi S, Dr. Gitansha Sachdev, Dr. D. Ramamurthy & Dr. Raline Solomon

*Abstract- Purpose:* To evaluate and compare the accuracy of Barrett Versus 3<sup>rd</sup> generation formulae for different intraocular lens (IOL) powers for Indian eyes with different axial lengths. *Setting:* The Eye Foundation Hospital, Coimbatore, Tamil Nadu, India- a tertiary eye care Center *Design:* Retrospective, Non-Randomized consecutive case series.

*Methods:* This study reviewed 981 eyes from 825 patients who had uneventful cataract surgery and IOL implantation. Eyes were separated into subgroups based on axial length as follows: short (<22.0 mm), medium (22.0 to 23.99 mm) and long (>24.0 mm). The predicted refractive outcome using formulas was calculated and compared with the actual refractive outcome to give the prediction error. The percentage of every refractive error absolute value for each formula was calculated at <±0.50D, 0.50D-0.75D and >±.75D.

GJMR-F Classification: NLMC Code: WW 354

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# Accuracy of Barrett Versus Third Generation Intraocular Lens Formula Across all Axial Lengths in Indian Eyes

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*Design:* Retrospective, Non-Randomized consecutive case series.

*Methods:* This study reviewed 981 eyes from 825 patients who had uneventful cataract surgery and IOL implantation. Eyes were separated into subgroups based on axial length as follows: short (<22.0 mm), medium (22.0 to 23.99 mm) and long (>24.0 mm). The predicted refractive outcome using formulas was calculated and compared with the actual refractive outcome to give the prediction error. The percentage of every refractive error absolute value for each formula was calculated at <±0.50D, 0.50D-0.75D and >±.75D,

*Results:* In all, 981 were analyzed. There were no significant differences in the median absolute error predicted by Barrett and the 3<sup>rd</sup> generation formulae. The Barrett Universal II formula resulted in significantly lowest mean spherical equivalent in short eyes (P=0.0047) as well as a higher percentage of eyes with prediction errors within<±0.50D, 0.50D-0.75D and >±.75D.We found that Barrett Universal II formula had the lowest predictive refraction error (PRE) and mean absolute error (MAE) across all axial lengths.

*Conclusion:* Barrett Universal II formula rendered the lowest predictive error compared with SRK/T, Holladay, and Hoffer Q formulas. Thus, Barrett Universal II formula may be regarded as a more reliable formula for achieving Emmetropia and reducing post-op refractive surprises across all axial lengths.

#### I. INTRODUCTION

he prediction of refractive outcomes after cataract surgery has steadily improved, with more recent intraocular lens (IOL) power formulas generally outperforming those of prior generations.(1,2) Yet there is still considerable debate about which formula provides the most accurate refractive prediction. Because no single formula has been shown to be highly

Author p: MD, Chairman and Head, the Eye Foundation Coimbatore Author  $\Omega$ : MBBS, DOMS. The Eye Foundation, Coimbatore. The Eye Foundation, 582, Diwan Bahadur Rd, R S Puram West, Coimbatore, Tamil Nadu 641002. India. e-mail: solomon ral@yahoo.co.in accurate across a range of eye characteristics, some authors have suggested that cataract surgeons should use different formulas for eyes of varied ocular dimensions.(3,4) Popular third-generation formulas (Hoffer Q, SRK-T, and Holladay 1) calculate effective lens position(ELP) using anterior chamber depth (ACD), axial length(AL) and keratometry (K). The Barrett Universal 2 formula uses a theoretical model eye in which anterior chamber depth (ACD) is related to axial length (AL) and keratometry. A relationship between the A-constant and a "lens factor" is also used to determine ACD. (5) The important difference between the Barrett formula and other formulas is that the location of the principle plane of refraction of the IOL is retained as a relevant variable in the formula.

The aim of this study was to investigate and compare the accuracy of Barrett Universal II formula for all axial lengths versus the Third generation formulae : SRK-T for long eyes (AXL>24mm), Holladay 1 for medium eyes (AXL=22-23.99 mm) and Hoffer Q for short eyes (AXL  $\leq 21.99$  mm) in predicting refractive outcome for standard cataract surgery.

#### II. PATIENTS AND METHODS

Study design: Retrospective, non-randomised case series

*Setting:* The Eye Foundation Hospital and postgraduate institute, Coimbatore, India

*Duration of data collection:* January 2017 and December 2018 (18 months)

The study adhered to the tenets of the Declaration of Helsinki and approved by the institutions ethics committee. Informed consent was obtained from all the participants included in the study. Patients with age related cataract undergoing uneventful cataract surgery were included in the study. Intra-operative complications, presence of any corneal pathology, glaucoma, retinal pathology, postoperative corrected distance visual acuity (CDVA) worse than 20/40, patients with preoperative corneal astigmatism of > 0.75D,eyes requiring additional surgical procedures at the time of cataract surgery (including peripheral corneal relaxing incisions), previous intraocular surgery (including previous refractive corneal surgery) were excluded from the final cohort.

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Ocular biometry was performed in all eyes using the IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany) based on swept-source optical coherence tomography (SS-OCT) technology. Patients were grouped into two groups, Group 1- Patients who had their IOL power calculated using Barrett universal Formula (Across all axial length) and Group 2- Patients who had their IOL power calculated using 3rd Generation IOL formulae(SRK-T for AXL≥24mm, what about ,Holladay 1 for AXL=22-23.99 mm and Hoffer Q for AXL≤ 21.99 mm. IOL power with the first myopic target refraction was selected for implantation All surgeries were performed by a single experienced surgeon using a 2.4 mm clear corneal incision and a standard Phacoemulsification technique. All patients had implantation of an AcryS of SN60WF intraocular lens (Alcon, Ft Worth, TX, USA). Preoperative examinations, operative details, postoperative findings, and refractive data were collected.

#### III. Statistical Methods

Refractive prediction error was considered as primary outcome variable. Groups (Group 1 vs. group 2) was considered as primary explanatory variable. All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution. For normally distributed Quantitative parameters the mean values were compared between study groups using Independent sample t-test (2 groups). P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.(6)

#### a) Statistical Analysis

The refractive prediction error was calculated as the difference between the postoperative refractive outcome expressed as spherical equivalent and the refraction predicted by each formula. A negative value indicates a myopic prediction error that shows a more myopic result than the predicted refraction. The mean numerical refractive prediction error for each formula, the mean absolute error (MAE) and median absolute error for each formula were calculated. The percentages of eyes within <  $\pm 0.50$  D, 0.50D-0.75D,>  $\pm 0.75$  D, of the predicted refraction were calculated and analyzed.

#### IV. Results

The study composed of 981 eyes of 825 patients. The demographics of the patients are listed in Table 1.

PARAMETER	STUDY GROUP (Mean± SD) AXL = 22.00-23.99 mm		P VALUE
	GROUP 1(N=404)	GROUP 2(N=337)	
K 1(D)	44.23 ± 0.87	44.74 ± 0.23	0.2842
K 2(D)	44.84 ± 0.80	44.71 ± 0.46	0.2574
AXL	22.80 ± 0.52	22.54 ± 0.13	0.1619
ACD	$3.02 \pm 0.23$	3.23 ± 0.12	0.1534
	STUDY GROUP (Mean± SD) AXL = ≥ 24 mm		
	GROUP 1(N=76)	GROUP 2(N=73)	
K 1(D)	43.2 ± 1.68	43.05 ± 1.32	0.5465
K 2(D)	43.55 ± 1.56	43.35 ± 1.33	0.4020
AXL	24.51± 0.21	24.81 ± 0.73	0.2805
ACD	3.55 ± 0.21	3.42 ± 0.10	0.3708
	STUDY GROUP (Mean± SD) AXL = ≤ 21.99 mm		
	GROUP 1(N=43)	GROUP 2 (N=48)	
K 1(D) 45.99 ± 1.58		46.15 ± 1.05	0.5672
K 2(D)	46.53 ± 1.44	46.47 ± 1.12	0.8240
AXL	21.55 ± 0.09	21.35 ± 0.05	0.1334
ACD	2.93 ± 0.24 2.88 ± 0.14		0.2223

Table 1: Pre-op patient demographics

Keratometry, AXL, ACD across all the study groups were comparable. There was almost no statistical difference on comparing post op Uncorrected distance visual acuity (UCDVA),refractive prediction

error(RPE),mean absolute error(MAE),CDVA across all the groups except a significant difference in mean refractive spherical equivalent(MRSE) in the group with short axial length as shown in Table 2.

PARAMETER	STUDY GROUP (Mean± SD) AXL = 22.00-23.99 mm		P VALUE
	GROUP 1(N=404)	GROUP 2(N=337)	
UCVA	$0.35 \pm 0.15$	0.33 ± 0.14	0.0629
MRSE	-0.19 ± 0.32	-0.14 ± 0.41	0.0628
RPE	-0.04 ± 0.20	-0.01 ± 0.43	0.2118
MAE	$0.20 \pm 0.04$	$0.24 \pm 0.10$	0.0660
CDVA	$0.00\pm0.00$	$0.00\pm0.00$	0.00
	STUDY GROU AXL = 2	IP (Mean± SD) ≥ 24 mm	
	GROUP 1(N=76)	GROUP 2(N=73)	
UCVA	0.13 ± 0.14	0.11 ± 0.1	0.3190
MRSE	-0.11 ± 0.3	-0.12 ± 0.3	0.8391
RPE	$0.07 \pm 0.31$	$0.04\pm0.35$	0.5801
MAE	0.24 ± 0.23	$0.26 \pm 0.24$	0.6042
CDVA	$0.02\pm0.08$	0.01 ± 0.04	0.3392
	STUDY GROU AXL =≤	IP (Mean± SD) 21.99 mm	
	GROUP 1(N=43)	GROUP 2 (N=48)	
UCVA	0.13 ± 0.11	0.16 ± 0.13	0.2407
MRSE	-0.1 ± 0.44	-0.23 ± 0.62	0.0047
RPE	$0.07 \pm 0.49$	$0.12 \pm 0.53$	0.6427
MAE	$0.33\pm0.37$	$0.39\pm0.38$	0.4485
CDVA	$0.00\pm0.08$	$0.00 \pm 0.02$	1

Table 2: Post- operative refractive parameters

However there was a good difference between the percentage prediction between the 2 groups, with the prediction error of Barret IOL formulae to be far superior and much closer to emmetropia than the other 3<sup>rd</sup> generation IOL formulae as shown in Tables 3 and 4.. There was no documented myopic or hyperopic surprise in any of the IOL formulae.

Table 3: Percentage prediction error using Barrett universal formula

	Long Eyes (%) (AXL ≥24.00mm) N=76	Normal Eyes (%) (AXL=22-23.99 mm) N=404	Short Eyes (%) (AXL≤ 21.99 mm) N=43
<± 0.50 D	96	92.3	90.6
0.50 – 0.75 D	1.3	4.7	4.6
> 0.75 D	2.6	3	4.6

Table 4: Percentage prediction error using 3rd Generation formula

	Long Eyes Srk-T (%) (Axl ≥ 24.00 Mm) N=73	Normal Eyes Holladay (%) (Axl 22-23.99 Mm) N=337	Short Eyes Hoffer Q(%) (Axl ≤ 21.9mm) N=48
± 0.50 D	93.1	82.5	75
0.50 – 0.75 D	6.8	7.9	8.3
> 0.75 D	0	6.2	16.6

#### V. Discussion

Corrected distance visual acuity has long been the principal outcome measure following cataract surgery; however, surgeons are now being judged more and more on refractive outcomes and the ability to achieve the desired refractive target and expected degree of spectacle independence. (7,8) Published results suggest that surgeons are, by and large, meeting expectations.(9,10) Refractive outcomes remain variable based upon differences in surgeon technique and experience, preoperative diagnostic technology and the population cohort.(11-14) Proposed benchmark outcomes also vary. Based on a large subset of patients undergoing surgery across the National Health Service, Gale and co-authors have previously suggested that 55% of patients should achieve postoperative spherical equivalent of  $\pm$  0.5D of the intended target and 85% of patients within  $\pm$  1.0D.(15) Subsequent papers however suggest outcomes in excess of these figures may be feasible. Simon et al achieved 67% of cases within  $\pm$ 0.5D and 94% of cases within  $\pm$  1.0D in their own case series located at an academic teaching institution.(16) Considering the combination of modern optical biometry, informed formula choice and IOL constant optimization, Sheard had proposed that surgeons should be able to achieve 60% and 90% within  $\pm$  0.5D and  $\pm$  1.0D respectively.(17) To determine the effectiveness of the IOL formula in a relatively standard population, we calculated the theoretical performance of Barrett Universal II in comparison with existing optimized formulas (Holladay I, SRK/T and Hoffer Q).

In our study, the prediction error of  $<\pm$  0.50D using Barrett universal formula across all axial lengths is given in Table 3. A Refraction prediction error of 96%, 92.3%, 90.6% in patients with Long, normal and short axial lengths was seen. In those whom 3rd generation formulae was used the prediction error of  $<\pm$  0.50 D was seen in 93.1%, 82.5%, 75% in patients with Long, normal and short axial lengths (Table 4). However there was no statistical significance in prediction error of patients in extreme of Axial lengths Long eyes p= 0.4360, Short eyes p=0.0525. The percentage of prediction error of  $< \pm$  0.50D in normal eyes between the Barrett and 3rd Generation formulae was statistically significant (p<0.0001). This difference in statistical significance could also be due large variation in the sample size across the three groups.

The mean absolute error derived from using Barrett Universal II were lower than those of the 3rd Generation formulae, across all axial lengths (Table 2). The real challenge in giving the best post-operative refractive outcomes lie in selecting the IOL formulae that would give the lowest refractive prediction error ,especially in eyes with extreme of axial lengths (AXL >24.00mm and <22.00 mm). In our study Barrett Universal II had prediction error of 0.07  $\pm$ 0.31, 0.07 $\pm$  0.49 versus 0.04±0.35,-0.12±0.13 using SRK=T, Hoffer-Q in long and short eyes respectively, the differences were not statistically significant and the results are almost comparable to those published by Zhou D et al and Gökce SE et al.(18,19) In terms of overall accuracy, the Barrett Universal II formula provided the equivalent or lowest variation within the data and thereby smallest percentage of refractive surprises compared to other formulas for all cohorts. Our results, representative of a standard non-toric Indian population show that excellent results can be achieved combining optical biometry with consistent technique and latest IOL power calculation formulas. The Barrett Universal II formula is independently available and require minimal additional manipulation to achieve excellent results across all axial lengths is a further benefit. Another advantage is that it does not require calculation of surgically induced astigmatism. The limitation of our study remains the relatively small numbers in the short and long axial length groups. Study inclusion was limited to the SN60WF IOL as this was one of most commonly used IOL in this part of the world. Although it would be reasonable to expect that the formulas would produce similar outcomes for additional lenses, further investigation may be useful to confirm this.

In conclusion, we found that excellent results can be obtained with a variety of IOL power calculation formulas for eyes with different axial lengths, especially extreme of axial lengths. The Barrett Universal II formula may provide additional benefits for patients by reducing possible refractive surprises and a very effective tool to reaching the goal of emmetropia which is a desirable goal for every cataract surgeon in the present day world.

a) What was known

Because there is no single highly accurate formula across a range of eye characteristics, many cataract surgeons should consider and use several formulas in eyes with various ocular dimensions.

b) What this paper adds

The Barrett Universal II formula is the most accurate predictor of postoperative refraction compared with the third generation across all axial lengths.

*Synopsis:* The Barrett formula appeared to have the least bias as measured by prediction error across all axial lengths, with better accuracy in shorter axial lengths.

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# Development and Validation of a *Yoga* Module for Adolescents with Type 1 Diabetes

By Sonu Maurya, Dr. Itagi Ravi Kumar, Dr. Amit Singh & Dr. R. Nagaratna

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*Abstract- Background:* Most adolescent patients with type 1 diabetes (T1D) do not meet treatment goals, which increases their risk for diabetes-related complications; therefore, finding ways to improve adherence to therapy is crucial. Yoga is known to more people as physical posture and a way to glycemic variability management strategy. The previous study has reported the beneficial role of yoga in improving glycemic variability and autoimmune disorder. However, a validated yoga module for T1D, is unavailable.

*Objective:* This study developed and validated a Junior yoga module (JYM) for adolescents with T1D.

*Materials and Method:* The content validity of JYM for adolescents is assessed by a panel of 20 experienced yoga experts. The JYM for adolescents with T1D is developed in the form of the tailor-made yoga practice supported by classical texts and research evidence. All the 41 practices in the JYM, is discussed and rated as:

## DEVELOPMENTANDVALIDATIONDFAYOGAMODULEFORADOLESCENTSWITHTYPEIDIABETES

Strictly as per the compliance and regulations of:



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# Development and Validation of a Yoga Module for Adolescents with Type 1 Diabetes

Sonu Maurya <sup>a</sup>, Dr. Itagi Ravi Kumar <sup>a</sup>, Dr. Amit Singh <sup>e</sup> & Dr. R. Nagaratna <sup>ω</sup>

Abstract- Background: Most adolescent patients with type 1 diabetes (T1D) do not meet treatment goals, which increases their risk for diabetes-related complications; therefore, finding ways to improve adherence to therapy is crucial. Yoga is known to more people as physical posture and a way to glycemic variability management strategy. The previous study has reported the beneficial role of yoga in improving glycemic variability and autoimmune disorder. However, a validated yoga module for T1D, is unavailable.

*Objective:* This study developed and validated a Junior *yoga* module (JYM) for adolescents with T1D.

*Materials and Method:* The content validity of JYM for adolescents is assessed by a panel of 20 experienced *yoga* experts. The JYM for adolescents with T1D is developed in the form of the tailor-made *yoga* practice supported by classical texts and research evidence. All the 41 practices in the JYM, is discussed and rated as:

- i. Not essential,
- ii. Useful but not essential,
- iii. Essential.

Lawshe's formula is adopted to arrive at the content validity ratio (CVR) after obtaining the ratings.

*Result:* Data analysis revealed that out of the 41 JYM practices, 27 JYM exhibited significant content validity (cut-off value: 0.49, as calculated by applying Lawshe's formula for the CVR).

*Conclusion:* The present study suggested that the JYM for adolescents with T1D is valid with good content validity. However, future studies must determine the feasibility and efficacy of the developed JYM module for adolescents with T1D.

Keywords: autoimmune disorder, type 1 diabetes, yoga and diabetes, yoga, adolescents.

#### I. INTRODUCTION

ost adolescent patients with type 1 diabetes (T1D) do not meet treatment goals, which increases their risk for diabetes-related complications; therefore, finding ways to improve adherence to therapy is crucial (Patel *et al.*, 2018). Type 1 diabetes (T1D) develops in genetically predisposed people as a result of the destruction of the pancreatic beta cells caused by an autoimmune insulitis (Briscoe *et al.*, 2007; Sharma, 2017). Increased thirst, frequent urination, bed-wetting in children and adolescents who previously didn't wet the bed during the night, extreme hunger, unintended weight loss, irritability and other mood changes, fatigue, and weakness, blurred vision are some major symptoms (Fowler, 2008; Kalra et al., 2013).

Adolescents experience significant physiological and psychosocial changes during this developmental stage, including increased insulin resistance related to pubertal hormones, significant weight gain, higher insulin needs, and independence from parents. Unfortunately, this newfound autonomy often results in problems with T1D. It may further exacerbate poor glycemic control. Besides, adolescents with chronic hyperglycemic conditions may be more likely to engage in high-risk behaviors, such as drug and alcohol use, cigarette smoking, etc. (Comeaux, 2010; Patel *et al.*, 2018; Weitzman *et al.*, 2015).

Yoga is a mind-body intervention and comprises physical practice (*äsana*), breathing technique (*präëäyäma*), and meditation, and relaxation techniques. Yoga is a popular complementary and alternative medicine modality worldwide (Falkenberg *et al.*, 2018).

Many studies have reported several health benefits of yoga for a clinical condition such as asthma. diabetes. pulmonary tuberculosis, epilepsy, fibromyalgia, and arthritis (Cramer, 2015; Gowtham, 2018; Hongasandra, 2017; Lin Yin et al., 2011; Nagothu, 2015; Patil, 2019; Ross & Thomas, 2010; Shantakumari et al., 2013; Vijayakumar, 2018; Vinutha et al., 2015; Zivdar, 2014), and consistent effects especially on circulating inflammatory markers (Falkenberg et al., 2018), improvements in physical fitness, immune activity (Kosuri & Sridhar, 2009), improved beta-cell function (Raj, 2016), and reduced stress as physiological mechanisms for beneficial effects of yoga on the immune system in adolescents (Sahay, 2007; Mohan et al., 2005; Szablewski, 2014).

#### II. QUALITY OF LIFE AND TYPE 1 DIABETES

Children with type 1 diabetes mellitus (T1DM) have to deal with a complex and demanding daily treatment regime, which can harm the quality of life (QoL) of these patients (Rasoul *et al.*, 2013). Although children and adolescents with T1DM have to live with a demanding treatment regime, overall results revealed that their generic QoL is not impaired compared to healthy peers (Duru *et al.*, 2015). Young adults with Type 1 diabetes mellitus are a high-risk group with suboptimal glycemic outcomes when compared with older adults with Type 1 diabetes (Ambler *et al.*, 2006). Management

is challenging because of psychosocial issues; for example, body image perceptions (Neumark et al., 2002), the increased incidence of psychiatric illness (Bernstein et al., 2013), eating disordered (Quick et al., 2012), and impaired quality of life (Kibbey et al., 2013; Ingerski et al., 2010). Some studies suggest that low glycemic variability may be associated with lower quality of life, negative moods, blood glucose fluctuations (Penckofer et al., 2012). A meta-analysis of 27 studies demonstrated that depression is majorly associated with hyperglycemia for type 1 diabetes (Lustman et al., 2000). Moods such as anxiety and anger often accompany depression with type 1 diabetes (Peyrot & Rubin, 1997); anxiety is associated with poor glycemic control (Anderson et al., 2002). Anger is also linked to depression (Pasquini et al., 2004). It is associated with glucose fluctuation and poorer self-management of hyperglycemia for persons with type 1 diabetes.

For persons with type 1 diabetes, high glucose values suggest to impact mood negatively, positive mood rating decreased, whereas negative mood ratings increased, tension and anger is reported to be higher in type 1 diabetes individuals in the hyperglycemic range compared with those in the hypoglycemic range with continuous glucose monitoring (CGM) (Hermanns et al., 2007). However, glycated hemoglobin (HbA1c) has been the standard for assessing glycemic control, glycemic variability (Hirsch, 2005).

#### III. Yoga and Immune System

Yoga is an ancient mind-body practice that is increasingly recognized to have health benefits in a variety of clinical and non-clinical conditions (Falkenberg *et al.*, 2018). Among various types of *yoga*, emphasizing both physical and mental training, and typically consists of *yoga* poses, breathing, and meditation (Nagendra, 2003). It is stated that *yoga* not only increased physical endurance but also reduced pro-inflammatory markers such as interferon  $\gamma$  (INF- $\gamma$ ), interleukin-6 (IL-6), interleukin-2 (IL-2), and stress level (Pullen *et al.*, 2008). Based on these results, *yoga* practice is required to achieve consistent effects, especially on circulating inflammatory markers (Falkenberg *et al.*, 2018), improvements in physical fitness, immune activity (Kosuri & Sridhar, 2009), improved beta-cell function (Raj, 2016), and reduced stress as a physiological mechanism for beneficial effects of yoga on the immune system (Sahay, 2007; Mohan et al., 2005; Szablewski, 2014). The practice of yoga reduced inflammation and smaller autonomic, endocrine, and inflammatory response to the stressors and novices. The yoga practice demonstrated more rapid declines (recovery) in stress hormone and proinflammatory cytokines production and better glycemic control in T1D (Sreedevi, 2017). Yoga is a cost-effective option in the treatment and prevention of autoimmune disorder, with data from several studies suggesting that yoga and other mindbody therapies can reduce stress-related hyperglycemia and have a positive effect on glycemic control, balancing harmonizing the body, mind, and emotions. Increasing evidence suggests that yoga practice tackles the pro-inflammatory mechanisms of T1D and helps in controlling autoimmune disorders (Amita et al., 2009: Author, 2019; Dubey et al., 2014; Sharma et al., 2013, 2014).

Previous studies on *yoga*, physical activity (Chimen *et al.*, 2012; De Lima *et al.*, 2017), and exercise (Herbst *et al.*, 2006; Reddy *et al.*, 2018) have demonstrated that these practices changed glycaemic variation, improved mental health and quality of life (QoL) in autoimmune diseases (Falkenberg *et al.*, 2018).

#### a) Materials and methods

The content validity of JYM for adolescents with T1D is assessed by a panel of 20 experienced *yoga* experts. The JYM for children and adolescents with T1D is developed in the form of tailor-made *yoga* practices that are supported by classical texts and research evidence.

All the 41 practices in the JYM, is discussed and rated as

i. Not essential,

ii. Useful but not essential,

iii. Essential.

Lawshe's formula is adopted to arrive at the content validity ratio (CVR) after obtaining the ratings.



The steps followed to execute the above-mentioned methods are as follows:

#### Step 1: Compilation of literature on yoga and diabetes

- a. In this phase, we reviewed traditional and contemporary *yoga* texts.
- b. Research paper on the use of *yoga* in diabetes, immune and metabolic disorders, including modern scientific reviews of T1D, were identified using different search engines such as Pub Med and Google Scholar. Indexing terms such as *yoga* immune disorder, metabolic disorder, and *yoga*, and diabetes. All experimental studies that used *yoga* as the therapy for diabetes are included.

#### Step 2: Shorting the literature on yoga and diabetes

A summary of the literature is tabulated for a quick overview. Then, studies done on different practices and published in journals as a scientific background is extracted.

Step 3: Preparing yoga module based on previous literature on yoga and diabetes

Based on classical texts and research evidence a detailed protocol with tailor-made practices is developed.

#### Step 4: Validation of JYM by expert

Yoga experts with clinical experience are provided with this complete module (who had either a doctorate or Doctor of medicine degree in *yoga*, with a minimum of 5 years experience or a Master's degree in *yoga/ yoga* therapist, with a minimum of 7 years experience). These experts were requested to participate in evaluating the content validity for the proposed instrument on a 3-point scale rated as follows: (i) not essential (has no role in improving any symptoms or the quality of life of patients with T1D), (ii) useful but not essential (useful in improving general wellbeing, but the benefits are not specific to T1D symptoms), and (iii) essential (very effective for T1D).

An expert panel, including 20 experts with the above qualifications, involved for determining the content validity. Experts in *yoga* therapy with clinical experience ≵5 years) were also considered *yoga* experts. Among the 20 experts, more than ten has previously applied *yoga* therapy in patients with diabetes and were already using most of the practice included in this module.

The CVR for the total scale was computed based on expert validation. According to Lawshe's formula, if more than half of the panelists indicate that an item is essential, then that item has the minimum content validity. The CVR for our scale was  $\geq$ 0.49, which was considered satisfactory for a panel of 20 experts.

b) Statistical Analysis

The cut-off value of 0.49 is calculated by applying Lowshe's formula for CVR (Lawshe, 1975). The mean CVR across the item indicated the overall test content validity.

$$CVR = \frac{n_e - N/2}{N/2}$$

Where,

Ne = total number of panelists indicating "essential" for each practice.

N = total number of panelist

#### IV. Result

The data analysis showed that out of 41 JYM practices, 27 indicated significant content validity in (Table 1). 14 practice (Table 2) had a CVR score of below 0.49, indicating low content validity.

SL. no.	Practice Name	CVR	SL. no.	Practice Name	CVR
1	Vyäghra Çväsana	0.9	15	Pavanamuktäsana	1
2	Pärçva Ürdhva Hastäsanä	0.5	16	Bhujaìgäsana	0.9
3	TäåäsanaPratyägama	1	17	Tiryaka Bhujaìgäsana	0.6
4	bhunamanPratyägama	0.7	18	Dhanuräsana	1
5	Naukäsaïcälana	0.9	19	Setubandhäsana	0.6
6	Süryanamaskära	1	20	Matsyäsana	0.5
7	Trikoëäsana	0.7	21	Naukäsana	0.7
8	Tiryaka Trikoëäsana	0.8	22	Uttänapädäsana	0.6
9	Pärçvakoëäsan	0.5	23	Çaväsana	1
10	Vakräsana	1	24	Anuloma- Viloma	1
11	Maëòükäsana	0.9	25	Bhrämaré	0.8
12	Garbhäsana	0.7	26	Guided Meditation on the Visualization of Pancreas	0.7
13	Üñöräsana	0.7	27	Agnisärakriyä	0.7
14	Bäläsana	0.5			

Table 1: Practice with a CVR score of  $\geq 0.49$ 

SI. No	Practice	CVR
1	Sasäìgäsana Çväsana (Rabit breathing)	0.3
2	Citrapataìga (Butterfly)	0.1
3	Dorsal stretch	0.2
4	Täåäsana	0.1
5	Véräsana	0.4
6	Jänusiräsana	0.3
7	Vyäghräsana	0.4
8	Ardhapädäpaçcimottänäsana	0.3
9	Kürmäsana	0.3
10	Bhardväjäsäna	0.3
11	Makaräsana	0.4
12	Çalabhäsana	0.3
13	Haläsana	0.4
14	Kapälabhäti	0.4

#### Table 2: Practices with a CVR score of $\leq$ 0.49.

Table 3: Yoga module for Adolescents with T1D

#### Special Yoga Module for Type 1 Diabetes Mellitus

Sl. no	Practice ( <i>Saà skrata</i> )	Practice (English)	Round	Time, minutes			
1. Starting Prayer (`shnavt u)							
2. 8	Specific <i>Kriyä</i> for Type 1 Dia	betes mellitus					
a. 🖌	a. Agnisära krivä 3 5						
3. 8	pecific loosening practice for	Type 1 Diabetes mellitus					
a.	Pärçva Ürdhva Hastäsanä	Side bending	5 each side	1			
b.	Täòäsanä Pratyägama	Mountain pose twist	5 each side	1			
с.	Bhünaman Pratyägama	Greeting the earth pose with twist	5 each side	1			
d.	Naukäsaï cälana	Rowing the boat flow	5	1			
4. 8	pecific breathing practice for	Type 1 Diabetes mellitus					
a.	Vyäghra Çväsana	Tiger breathing	5 up & down	1			
5. 3	Süryanamaskära (Slow speed	<b>1</b> 3 to 6 round according to a	an individua	l's capacity)			
6. 8	pecific relaxation after breat	hing					
a.	<i>Çaväsana</i> (with "A-kar" chanting)	Quick relaxation technique	1	1-2			
7. 8	Specific Standing <i>Äsana</i> for '	Type 1 Diabetes mellitus					
a.	Trikoëäsana	Triangle Pose	1	1			
b.	Tiryaka Taòäsanaa	Mountain Pose	1	1			
с.	Pärçvakoëäsana	Side Angle Pose	1	1			
8. 3	8. 30 second relaxation after each <i>Äsana</i> (as per the condition)						
9. 8	9. Specific Seating <i>Äsana</i> for Type 1 Diabetes mellitus						
a.	Vakräsana	Spine twist pose	1	1			
b.	Maëòükäsana	Frog pose	1	1			
с.	Garbhäsana	Embryo pose	1	1			

d.	Üñöräsana	Camel pose	1	1			
e.	Bäläsana	Child pose	1	1			
f.	Pavanamuktäsana	Wind relieving pose	1	1			
10.3	0 second relaxation after each	n Äsana (as per the conditio	<i>n</i> )				
11. S	pecific Supine <i>Äsana</i> for Ty	pe 1 Diabetes mellitus					
a.	Setubandhäsana	Bridge pose	1	1			
b.	Matsyäsana	Fish pose	1	1			
с.	Naukäsana	Boat pose	1	1			
d.	Uttänapädäsana	Raised leg pose	1	1			
12.3	12. 30 second relaxation after each Äsana (as per the condition)						
<b>43.</b> S	p <b>®kidje/Pgäsen</b> aÄ <b>sana</b> for Typ	eCoDiapotes mellitus	1	1			
b.	Tiryaka Bhujaì gäsana	Swaying cobra pose	1	1			
1. S	pecific relaxation after Äsar	a for Type 1 Diabetes					
a.	Çaväsana	Dep relaxation technique	1	5			
2. S	pecific Pranayama for Type 1	l Diabetes mellitus					
a.	Anuloma-Viloma	Alternate nostril breathing	9	5			
b.	Bhrämaré	Bee sound	9	5			
3. S	3. Specific Meditation for Type 1 Diabetes mellitus						
a.	Guided Meditation on the Visualization of Pancreas		1	10			
4. 0	Closing prayer (s vۃvN uz io n>	)					
			Time	e duration – 60 min			

#### V. DISCUSSION

In the present study, we developed a JYM for adolescents with T1D by choosing specific yoga practices from the traditional literature and scientific studies on yoga to target certain symptoms of adolescents with T1D. Validated JYM by the yoga experts taking their suggestions is finalized. Similarly, an effort was made to retain only those practices which were rated by all experts as useful. The yoga practices are included, as suggested by the experts. All the experts opined that these practices should be easy for children and adolescents with T1D. Relaxation practice is also included between the session as per the advice of the experts. So, The matching of yoga practices with symptoms of adolescents finalized after reviewing traditional literature (Saraswati, 2004; Mukibodha, 2000). The present study was closely associated with previous studies on the validation of JYM (Ahilan, 2015; Amita et al., 2009; Author, 2019; Balaji et al., 2012; Baro, 2016; Berger et al., 1977; Chandrasekhar, 2009; Dubey et al., 2014; Eda, 2014; Kudigra & Ns, 2018; Kumar, 2017; Kumar, 2015; Metri et al., 2017; Prabhu et al., 2015; Raj, 2016; Raveendran et al., 2018; Rodrigues, 2016; Sharma et al., 2013, 2014; Shrivastava et al., 2017; Vaishali et al., 2012; Campaigne, 1985).

In the present, there is no previous study that focused on the validation of a yoga module for T1D. This study is done in two phases:

a) We are designing the yoga module for T1D, b) expert validation of the module for T1D.

In the first phase, the JYM was designed based on literature reviews of traditional text reference and recent research publications. We did not find any direct source for yogic practice capable of improving T1D symptoms. However, the latest Hatha Yogic text has increasingly emphasized on improving health through different yogic practices. Besides, recent findings on T1D reported by several schools of yoga have helped in the formulation of a yoga module for T1D. The CVR calculation for all 41 practices is completed in our voga module. Of these, 27 practices (CVR≥0.42) were included in the validated yoga module (Table 1). The remaining fourteen poses (Table 2) (CVR <0.49), namely Butterfly, Tadasana, (0.1), Dorsal stretch (0.2), Rabit breathing, Janusirasana, Ardhapadapaschimittanasana, Kurmasana. Bharadwajasana, Salabhasana (0.3), Veerasana, Vyaghrasana, Makarasana, Halasana, Kapalbhati (0.4) were used as a complementary for important posture to stimulate the pancreases and synchronization along with body and mind. These practices were slightly challenging for T1D therapy. Apart from these fourteen practices, the 27 poses included for T1D treatment; thus, the final CVR satisfied the minimum value, as per Lowshe's CVR.

Similar to any other exercise protocol, an ideal yoga module consists of frequencies, intensities, duration, and progression. Determining the appropriate mode depends upon the patient's preference and safety issues associated with the T1D or other conditions. Keeping in view the safety and patient's ability the duration and frequency of the pose customized for practice (Table 3).

*Çithilikaraëa Vyäyäma* (Loosening Practice) include in this module helped in loosening the joint and strengthen the muscles, which consequently helped in improving the function of abdominal organs (Dhirendra, 1973).

*Süryanamaskära* (Sun Salutation), A series of dynamic *yoga* posture in a specific sequence, stimulate insulin production through brain signaling, exerting beneficial effects on the glycemic outcome (Raj, 2016).

Yogäsana (Yoga Posture) rejuvenates of pancreatic cells through the alternating abdominal contraction and relaxations involved in *yoga* practice. Improves blood supply to muscles, enhances insulin receptors expression in the muscles, with forwards bending pose, manage and pressurizing the pancreas, stimulating insulin secretion (Ahilan, 2015; Eda, 2014).

*Çuddhikriy*ä (Cleansing Processes), *Agnisära Kriy*ä (stimulating the digestive fire) involves pulling the abdomen in and snapping it backward and forward while holding one's breath. Helps in the producing of insulin and controlling glucose levels in the blood; the effect of this action massage the internal organs and increases blood flow to the area (Kudigra, 2018; Raveendran *et al.*, 2018).

*Präëäyäma* (regulated breath), *Anulomvilom* (alternate nostril breathing), improves components of health-related fitness, cardio respiratory endurance, flexibility, and body fat percentages.

*Bhrämaré* (humming bee breath), a soothing and calming effect on the mind, improves mental and physical health(Author, 2019; Sreedevi, 2017).

*Dhyäna* (Meditation): This leads to beneficial psychological effects, such as a faster reaction to stimuli and less prone to various forms of stress, anxiety reduction, and blood pressure control. Meditation on the *Manipur Chakra* (solar plexus), visualization of the pancreas during meditation, gives positive effects on sugar levels (Balaji *et al.*, 2012; Eda, 2014; Raj, 2016).

#### VI. Conclusion

A comprehensive and traditional texts based *yoga* module was developed and validated by 20 experts who agree to most of the practices. Whoever, future studies must determine the feasibility and efficacy of T1D.

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## Global Journals Guidelines Handbook 2020

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## MEMBERSHIPS FELLOWS/ASSOCIATES OF MEDICAL RESEARCH COUNCIL FMRC/AMRC MEMBERSHIPS



#### INTRODUCTION

FMRC/AMRC is the most prestigious membership of Global Journals accredited by Open Association of Research Society, U.S.A (OARS). The credentials of Fellow and Associate designations signify that the researcher has gained the knowledge of the fundamental and high-level concepts, and is a subject matter expert, proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice. The credentials are designated only to the researchers, scientists, and professionals that have been selected by a rigorous process by our Editorial Board and Management Board.

Associates of FMRC/AMRC are scientists and researchers from around the world are working on projects/researches that have huge potentials. Members support Global Journals' mission to advance technology for humanity and the profession.

## FMRC

#### FELLOW OF MEDICAL RESEARCH COUNCIL

FELLOW OF MEDICAL RESEARCH COUNCIL is the most prestigious membership of Global Journals. It is an award and membership granted to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Fellows are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Fellow Members.

## Benefit

## To the institution

#### GET LETTER OF APPRECIATION

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#### GET ACCESS TO A CLOSED NETWORK

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#### CERTIFICATE

#### Certificate, LOR and Laser-Momento

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#### DESIGNATION

#### GET HONORED TITLE OF MEMBERSHIP

Fellows can use the honored title of membership. The "FMRC" is an honored title which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., FMRC or William Walldroff, M.S., FMRC.



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areer Financial



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## AMRC

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## CERTIFICATE

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Career	Credibility	Exclusive	Reputation



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All the Associate members of AMRC get a badge of "Leading Member of Global Journals" on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation.





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Exclusive Financial

## REVIEWERS

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- 2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
- 3. Ensure corresponding author's email address and postal address are accurate and reachable.
- 4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
- 5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
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- Findings
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- 3. Final approval of the version of the paper to be published.

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#### Acknowledgments

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



#### Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11<sup>1</sup>", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

#### Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- 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.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

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



## Format Structure

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

All manuscripts submitted to Global Journals should include:

#### Title

The title page must carry an informative 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) where the work was carried out.

#### Author details

The full postal address of any related author(s) must be specified.

#### Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

#### Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

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

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning 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 a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

#### **Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

#### Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

#### Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

#### Tables, Figures, and Figure Legends

Tables: Tables should be 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. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

#### Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

### Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). 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.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

#### TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

**1.** *Choosing the topic:* In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

**2.** *Think like evaluators:* If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. 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.

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

**4.** Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

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

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

**8.** *Make every effort:* Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

**9.** Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

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

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

**12.** *Know what you know:* Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

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Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

**14.** 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 for your topic. You may also maintain your arguments with records.

**15.** Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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

**17.** *Never copy others' work:* Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

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

**19.** *Refresh your mind after intervals:* Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

**20.** *Think technically:* Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

**21.** Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

**22. Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

**23. Upon 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 though which your research is going to be in print for 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 of 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 criteria peer reviewers will use for grading the final paper.

#### **Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

#### The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to 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 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.



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#### Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

#### Title page:

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

**Abstract:** This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite 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 approaches 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. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a 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 limit the initial two items to no more than one line each.

#### Reason for writing the article—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 for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

#### Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- o Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity 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 of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- o Briefly explain the study's tentative purpose and how it meets 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 for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory 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 soundly written procedures segment allows a capable scientist to replicate 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 to give the least amount of information that would permit another capable scientist to replicate 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 section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show 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:

Materials may be reported in part of a section or else they may be recognized along with your measures.

#### Methods:

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

#### Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and 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.
- o 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 as 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. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

#### Content:

- o Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- o In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give 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 manuscript.

#### What to stay away from:

- o Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- o Do not present similar data more than once.
- o A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

#### Approach:

As always, use past tense when you submit 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 section.

#### Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

#### Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an 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 implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully 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 the prospect, and let it drop at that. Make a decision as to whether each premise is supported or 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 an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- o Recommendations for detailed papers will offer supplementary suggestions.

#### Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	А-В	C-D	E-F
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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