Reprint from The Review of DIABETIC STUDIES Vol 19 No 2 2023

The Review of DIABETIC STUDIES

RESEARCH

Symptomatic Characteristics and Screening of Retinopathy of Prematurity: A Systematic Review

Elizabeth Ndunge Mutua[1], Bernard Shibwabo Kasamani[1], Christoph Reich[2]

[1]School of Computing & Engineering Sciences, Strathmore university, Kenya. [2]Institute for Data Science, Cloud Computing and IT Security, Furtwangen university, Germany. Address correspondence to: Elizabeth Ndunge Mutua, Email: Elizabeth.mutua@strathmore.edu

Manuscript submitted May 15, 2023; resubmitted May 31, 2023; accepted Jun 28, 2023

■ Abstract

Background: Retinopathy of Prematurity (ROP) is a retina vascular disorder which affects infants. ROP occurs because of immature retina tissues which develop abnormally. The diagnosis of the disease involves an ophthalmologist conducting an examination of the retina to identify the presence of the abnormally growing vessels. Deep Learning applications have widely been developed for ROP disease diagnosis and their development suffers numerous challenges. Aim: To establish current global ROP statistics, ROP disease screening guidelines within Africa, the current rate of preterm births in Africa and the challenges associated with Deep Learning applications for the disease diagnosis. **Methods:** A database search (Ovid, PubMed, Science Direct, Embase, Web of Science, AJOL, MEDLINE, CINAHL, Google Scholar) was performed to identify relevant articles that were published up to October 2022. PRISMA guidelines of academic papers review were followed to ensure that all included articles had reported their study methodological elements as well as meeting their objectives where forty-five articles were included. **Results and Conclusions:** The results reveal that there are few studies published from the period 2018 to 2022. South Africa and Kenya are the only countries in Africa with national ROP screening guidelines. Deep Learning systems can effectively be applied to assist ophthalmologists in accurately diagnosing the disease however, proper development and testing of these systems is required. The information in this review may help to guide future studies on ROP disease screening in Africa as well as pointing out the challenges of Deep Learning systems for the disease diagnosis.

Keywords: ROP Classification, Screening Procedure, ROP Diagnosis, Birth Weight, Gestational Age.

1. Introduction

Retinopathy of Prematurity (ROP) is an eye disorder which arises because of abnormal growth of blood vessels in the retina of babies born prematurely [1]. The disease affects babies born before week thirty-one (31) of pregnancy and with a weight of less or equal to 1500 grams at the time of birth [2]. Retina vessels begin to develop at 16th week of pregnancy and are completed at 36th week. Babies born before 36th weeks have their retina vessels not fully developed and sometimes some babies will have their vessels develop while others may not [3]. If the vessels do not develop and the problem is not detected, the disease progresses to later severe stages and the baby goes blind. ROP continues to be a global disease whose cases continue to increase yearly. The aim this paper is to present the pathogenesis of the disease, disease classification, ROP cases incidents from Africa and non-Africa countries as well as preterm cases. The findings of this work can be used by most of the countries within Africa who have no screening guidelines in the development of the guidelines.

1.1. Pathogenesis of ROP

The blood vessels of the retina begin to develop at sixteen (16) weeks of pregnancy and the development is completed after forty (40) weeks [4]. When a baby is born pre-term, retina vessels do not develop normally. Some blood vessels stop developing, then suddenly start developing abnormally [5]. The abnormal retinal vascular development towards the wrong direction starts to pull the retina from the back of the eye. If diagnosis is not done in good time, then the retina detaches, and the baby goes blind [6].

1.2. Classification of ROP

Retinopathy of Prematurity Zones and stages is categorized using a classification provided by the International Classification of ROP (ICROP) which was published in 1984 [7] and revised in the year 2005 [8]. The disease is classified within three retina zones as shown by Figure 1, which is used to determine the leading edge of the retina vascularization and the stage of the disease [9]. Zone 1 is a circular area within the optic disk, and its radius is twice the distance between the macula and the optic disk. Zone 2 is a circular area

within the optic disk, but its circumference extends to the nasal ora serrata. The last zone, which is zone 3, is the remaining area after zone 2. ROP in Zone 1 is considered to become aggressive and severe while in Zone 3 is less aggressive and less severe.

ROP disease has five stages as shown by Figure 2 [11]. Stage 1 is termed as the initial stage and during this stage, a neonate eye develops a thin demarcation white line separating the retinal regions of the eye and hence preventing flow of blood to the rest of the eye [11]. This occurs because of the abnormal growth of blood vessels. If not detected and treated, the demarcation line grows thicker forming a pinkish ridgeline and this becomes stage 2 [12]. In stage 3 the pinkish ridgeline grows broader resulting in the formation of blood vessels abnormality [12]. Stage 4, which is an advanced stage, the retina detaches partially and the extraretinal neovascularization slowly begins to cause traction on the retina [12]. Stage 5, The retina detaches completely, and the baby goes blind. Stage 1 and 2 of ROP can heal without any medical intervention but diagnosis at stage3 is important to stop its progression to stage 4, for stage5 where the baby goes blind, a whitish spot can be seen on the eye [12]. The presence of severe ROP is also termed as Plus disease and occurs when the retina detaches completely because of increased vessels dilation and arteriolar tortuosity of the posterior pole vessels [11].

1.3. ROP Diagnosis Procedure

Dilating drops are put on the eyes of the infant which enables an ophthalmologist to clearly view the retina [2]. A speculum is required to hold the eye of the baby because they cannot hold open their eyes for a long time [6]. A depressor is used to direct the eye to provide a better view while a bright light is supplied for clarity. An ophthalmologist checks on the retina to determine if the baby has ROP or not [12]. For hospitals without an ophthalmologist, or for cases where a hospital has many babies requiring examination and only one ophthalmologist is available, an image of the eye is taken using fundus camera, printouts of the image is done and send to an ophthalmologist for diagnosis [12].

Abbreviations:

ROP	Retinopathy of Prematurity
DL	Deep Learning
BW	Birth Weight
GA	Gestational Age

2. Literature Review

This section presents ROP cases for non-African countries as well as for Africa countries. We also review the preterm cases within Africa together with countries within Africa with ROP screening guidelines.

2.1. ROP Cases for Non-african Countries

As shown by Table 1, in the United States, ROP incidents cases increased from 11% to 15% from the years 2009 and 2018 for a population of 717,277 and BW>1500 g or GA>30 weeks [13]. For South Korea a study done between the years 2007 and 2018 for a population of 141,964, ROP cases were at 29.8% where GA was 28 weeks≤GA<37 weeks [14]. In Turkey, a study done within 69 Neonatal Intensive Care Units and between April 2016 up to April 2017 for dataset of 6,115, ROP cases were 27% and 6.7% had severe ROP stage where GA was BW>1500 g or GA>32 weeks [15]. In Canada, a study done for the years 2010 up to 2016 at McMaster Children's Hospital for a dataset of 623 showed that ROP cases were 67.1% and GA was GA from 24 weeks to < 34 weeks [16].

A study done in Brazil for the years 2015 up to 2017 at a hospital in the city of São Paulo, ROP cases were 26.4% for a dataset of 288 and the GA was GA

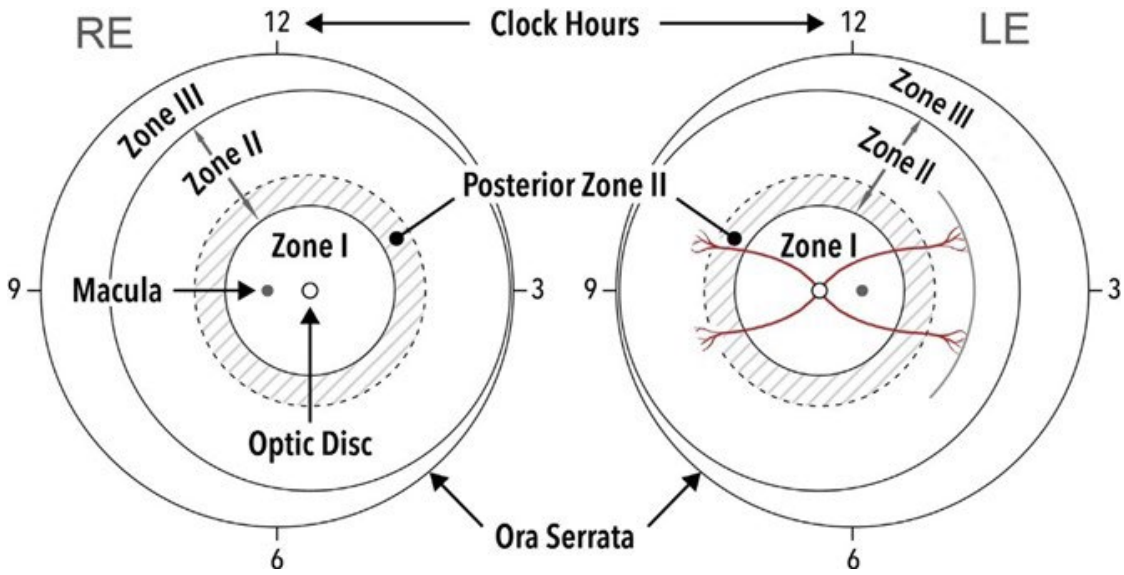

Figure 1: ROP Zones [10].

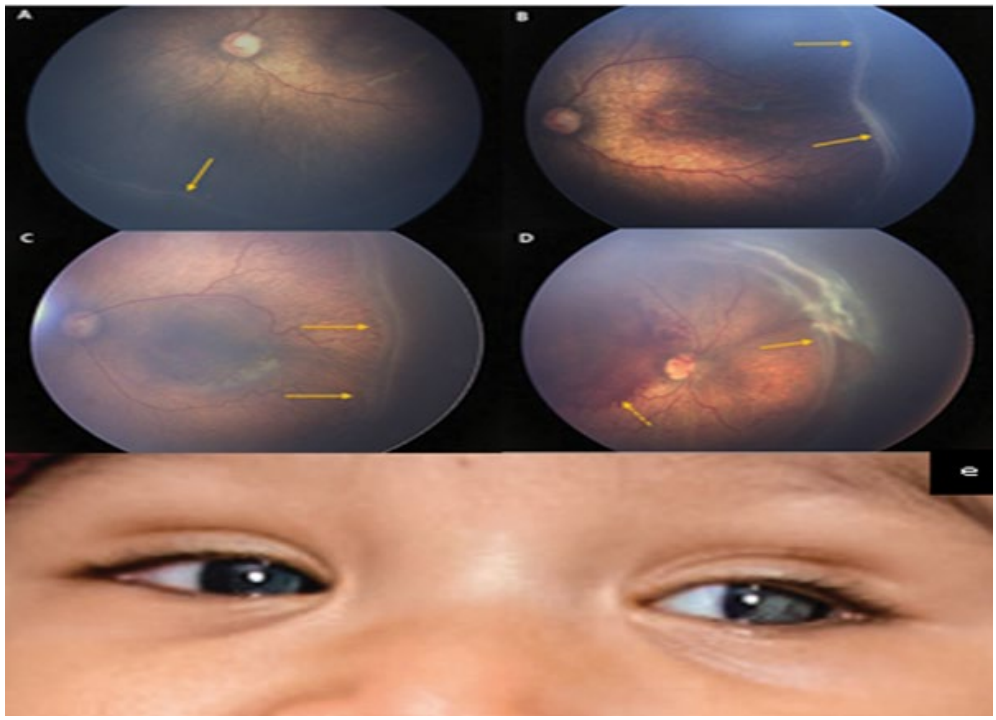

Figure 2: Retinopathy of Prematurity Stages. In Stage 1, a Demarcation Line Begins to Grow (a), in Stage 2, the Demarcation Line Becomes an Elevated Ridge (b), Stage 3 the Ridgeline Grows Thicker and Abnormal Blood Vessels Growth Can Be Seen (c), Stage 4 Partial Retinal Detachment is Seen (d) Then Stage 5 the Infant Goes Blind and There is a Whitish Substance Seen on the Eye(e) [10].

Table 1: ROP Cases on Population-Based Studies for Non-african Countries.

Study	Period	Database	Study Population	Gestational age	ROP Percentage
Thangamathesvaran *et al.* [13], US	2009-2018	National Inpatient Sample	717,277	BW>1500 g or GA>30 weeks	15%
Hong *et al.* [14], South Korea	2007-2018	population-based National Health Insurance database	141,964	(GA)<37 weeks (GA<28 weeks, GA28; 28 weeks≤GA<37 weeks; GA28-37)	29.8%
Bas *et al.* [15], Turkey	Apr 2016-Apr 2017	Data collected from 69 neonatal intensive care units (NICUs)	6115	BW>1500 g or GA>32 weeks	27%
Isaza *et al.* [16], Canada	2010-2016	Data collected from (NICU) at McMaster Children's Hospital	623	GA between 24 weeks and < 34 weeks	67.1%
Martins *et al.* [17], Brazil	2015-2017	hospital in the city of São Paulo	773	GA <=34 weeks	26.4%
Sanghi *et al.* [18], India	January 2018-December 2020	level IIIA NICU	211	BW<2000 or GA<34	21.8%
Sabherwal *et al.* [19], India	March-May 2017	Four hospitals in India	157	BW ≤2000g or GA < 34 weeks or GA 34 and 36 weeks if exposed to other factors of illness	11%
Alda *et al.* [20], Argentina	2004-2016	Database owned by the ROP Argentina Group	2739	BW>1500 g	22.7%
Sidorenko [21], Russia	Oct 2016-Nov 2017	Scientific and Practical Center of Pediatric Specialized Medical Care in Moscow	132	GA 27.62 +- 2.44 weeks	71.97%
Li *et al.* [22], China	2016-2021	Tianjin Eye Hospital	4069	GA >=29.1<=32.9	17.9%
Shiraki *et al.* [23], Japan	Sept 2009-May 2017	Data collected from (NICU) at Children's Hospital	692	BW<=2000 g or GA <=34 weeks	77.6%
Yucel *et al.* [24], Turkey	Jan 2012-Dec 2020	Data collected from Ondokuz Mayis University Hospital	2186	BW (≤1000 g, 1001-1750 g, >1750 g) and GA (≤25w, 26-28w, 29-31w, 32-34w, ≥35w)	43.5%
Trzcionkowska *et al.* [25], Netherlands	2017	Leiden University Medical Center	1492	GA<32	20.4%

Legend: BW- Birth weights; GA- Gestational Age

<=34 weeks [17]. In India, we found two most recent studies [19], did a study in four hospitals for a period of three months (March up to May 2017) and a dataset of 157 infants, ROP cases were 11% and the GA was BW ≤2000g or GA < 34 weeks or GA 34 and 36 weeks if exposed to other factors of illness while Page *et al.* [26] did a study for the period between January 2018 up to December 2020, for a dataset of 211 where the ROP cases percentages were at 21.8% and BW<2000 or GA<34. For Argentina, a study done by Alda *et al.* [20] for the period between the years 2004 up to 2016 and with a dataset of 2,739, ROP cases were at 22.7% where BW was BW>1500 g. For Russia, a study done for the period between October 2016 up to November 2017 fora dataset of 132, ROP cases were at 71.97% and the GA was GA 27.62 +- 2.44 weeks [21].

In China, a study done for the period between the years 2016 up to 2021 and a dataset of 4,069 obtained at Tianjin Eye Hospital, ROP cases were at 17.9% for a GA of GA>=29.1<=32.9 [22]. In Japan, data collected from a Neonatal Intensive Care Unit (NICU) at Children's Hospital for the period between September 2009 up to May 2017 and a dataset of 692, ROP cases were at 77.6% and GA was BW<=2000 g or GA <=34 weeks [23]. In Turkey, a study done for the period between January 2012 up to December 2020 with a dataset of 2,186, ROP cases were 43.5% and GA was BW (≤1000 g, 1001-1750 g, > 1750 g) and GA (≤25w, 26-28w, 29-31w, 32-34w, ≥35w) [24]. In the Netherlands, a study done year 2017 at Leiden University Medical Center and a dataset of 1,492, ROP cases were 20.4% and the GA was GA<32 [25].

2.2 ROP cases for African countries

We found eight (8) most recent studies on population-based cases of the disease within Africa as shown by Table 2. In Nigeria, a study done by Ademola-Popoola *et al.* [27] between the year 2017 up-to 2018 and a population of seven hundred and twenty-three (723), ROP cases were at 17.6% and the screening criteria was GA <34 weeks or birth weight ≤2000 g, or sickness criteria. In Ethiopia [28] a study for the period between June 2016 up-to august 2019 for a population of sixty- six (66) infants, ROP cases were 42.4% and the screening criteria was GA 28.4±1.6 or BW 1172.7±259.6. In Egypt, ROP cases were at 34.1% for the period between 1st to 31st October 2020 for a dataset of two hundred and forty (240) infants, the screening criteria was GA) ≤34 weeks or birth weight (BW) ≤2000 g or infants with unstable course [29]. In Ghana, a study done by Braimah *et al.* [30] for the period between June 2018 up to February 2019, and a population of four hundred and one (401), ROP cases were 13.7% and the screening criteria was BW< 2 kg or GA < 37 weeks.

Table 2: ROP Cases on Population-based Studies for African Countries.

Study	Period	Database	Study Population	Gestational age	ROP Percentage
Ademola-Popoola *et al.* [27], Nigeria	2017-2018	Data collected from 84 public neonatal units	723	GA <34 weeks or birth weight ≤2000 g, or sickness criteria	17.6%
Melesse [28], Ethiopia	June 2016-August 2019	WGGA eye center database	66	GA 28.4±1.6 or BW 1172.7±259.6	42.4%
Noor *et al.* [29], Egypt	1st October -31st October 2020	Database for an NICU in Itay Elbaroud City, Behera province	240	GA) ≤34 weeks or birth weight (BW) ≤2000 g or infants with unstable course	34.1%
Braimah *et al.* [30], Ghana	June 2018-February 2019	Data collected at an NICU of Korle-Bu Teaching Hospital (KBTH).	401	BW< 2 kg or GA < 37 weeks	13.7%
Seobi *et al.* [31], South Africa	1st January 2015-31st June 2020	Data collected at central and non-central hospitals in Johannesburg	1081	GA < 28 weeks, or BW < 1500	24.3%
Onyango *et al.* [10], Kenya	January 2010-December 2015	Nairobi Hospital database	163	GA 29.9 ± 2.2 weeks and the mean BW 1280.1 ± 333.0 grams.	41.7%
Epee Ngoue *et al.* [32], Cameroon	January 2013-December 2017	Data From maternity ward of Hôpital Central de Yaoundé (HCY), Hôpital Gyneco-Obstétrique et Pédiatrique de Yaoundé (HGOPY), and Centre Hospitalier d'Essos (CHE)	5640	GA 22-37 weeks	14.8%
Mutangana *et al.* [33], Rwanda	September 2015-July 2017	Data Collected from King Faisal Hospital (KFH) and University Teaching Hospital of Kigali (CHUK), and one in Huye, University Teaching Hospital of Huye (University of Rwanda campus Butare, CHUB)	424	GA<35 weeks or BW<1800	7.3%

Legend: BW- Birth Weights; GA- Gestational Age

A study done by Seobi *et al.* [31] in South Africa from 1st January 2015 up to 31st June 2020 for a population of one thousand and eighty-one (1,081) infants, ROP cases were at 24.3% and the screening criteria was GA < 28 weeks, or BW < 1500. In Kenya, for the period between January 2010 up to December 2015, ROP cases were at 41.7% for a dataset of one hundred and sixty-three infants (163), and the screening criteria was GA 29.9 ±2.2 weeks, BW 1280.1 ± 333.0 grams [10]. A dataset of five thousand, six hundred and forty (5,640) infants collected from three hospitals in Cameroon showed that ROP cases were 14.8% and the screening criteria was

GA 22-37 weeks [32]. In Rwanda, the period between September 2015 up to July 2017, data collected from three hospitals and of size four hundred and twenty-four (424) infants, ROP cases were 7.3% and the screening criteria was GA < 35 weeks or BW < 1800 [33].

2.3. Preterm cases and ROP screening guidelines within Africa

As shown by Table 3, there seemed to be not much recent studies done within Africa about the rates of preterm Births. Kenya and South Africa are the only two countries in Africa with national screening guidelines [34]. Nigeria for the period between 1st January 2008 up-to 31st December 2015 and a data size of 1,129, the preterm births were at 32.9%, [35]. For Ethiopia, a study done from February to April 2020 reported preterm births were at 11.4% for a dataset of 482, [36]. For Egypt, as reported by Algameel *et al.* [37], preterm births percenta ge were at 28% for a dataset of 250 births for the period between May to November 2018. Ghana for the period between October to December 2018 reported 14.1% preterm births for a dataset of 680, [38]. South Africa as reported by Jeena *et al.* [39], for a dataset of 760, reported preterm births at a percentage of 16.4% for the period between April 2013 up to March 2018. Kenya for the period from 1st October 2013 up to 31st March 2018 and a dataset of 16,966, preterm births were at 12.6% [40]. Epee Ngoue *et al.* [32] reports 14.8% preterm births for Cameroon for a dataset size of 38,151 for the period between January 2013 up to December 2017. In Rwanda, for the year 2018 and a dataset of 363,000 reported preterm births of 10% [35]. Uganda reported preterm births of 13.4% for a dataset of 34,015 for a study done between 1st October 2016 up to 31st March 2018, [40].

Table 3: Preterm Births and ROP Screening Guidelines Availability Within African Countries.

Study	Study Period	Data size	Preterm Percentage	ROP Screening Guideline
Mustapha *et al.* [36], Nigeria	1st January 2008-31st December 2015	1,129	32.9%	None
Adugna [34], Ethiopia	February-April 2020	482	11.4%	None
Algameel *et al.* [37], Egypt	May-November 2018	250	28%	None
Axame *et al.* [38], Ghana	October – December 2018	680	14.1%	None
Jeena *et al.* [39], South Africa	April 2013-March 2018	760	16.4%	Available from Year 2013
Waiswa *et al.* [40], Kenya	1st October 2016-31st March 2018	16,966	12.6%	Available From year 2018
Epee Ngoue *et al.* [32], Cameroon	January 2013- December 2017	38,151	14.8%	None
Every Preemie—SCALE [35], Rwanda	2018	363,000	10%	None
Waiswa *et al.* [40], Uganda	1st October 2016-31st March 2018	34,015	13.4%	

2.4. Deep Learning Applications for ROP Disease Diagnosis Challenges

Deep Learning applications work best when trained with an accurately labelled dataset. An error in labelling the images can result to misdiagnosis of the disease. Lack of proper training for clinicians about Artificia l Intelligence models, makes them not be in a position to detect model biasness [41]. This could cause harm and misleading diagnosis results [42]. Getting Deep Learning applications off the research shelves and integrating them into real-life clinical use and practice has been an uphill task for most researchers. The fear of misdiagnosis by DL algorithms has made it impossible to have these applications beingused at eye clinics today. Currently, we only have a few of them being used for the disease diagnosis and screening which are externally validated [42]. There exist also few studies to compare cost- benefits of adopting these models for the disease diagnosis, [43] which we believe when done can pave way through creating awareness of their benefits, adoption and use.

The challenges of retinal imaging include the gold standard imaging modality for photography. The provided standard photography provides a narrow field of view of about 2 to 3 disc diameter or a magnification of the image which is bigger than the indirect ophthalmoscopy. This can affect the accuracy of the Deep Learning model which learn from the data provided to make decisions [43]. A key challenge with using the standard photography for diagnosing ROP Plus disease is that the images appear more dilated with less tortuosity than the actual eye image, this calls for ICROP committee to provide images to define the minimum abnormality for the Plus disease. Different lighting background also can produce images of different color shades. This variation results to errors or wrong images being used for training the model and has a negative impact on the results [44].

3. Methodology

3.1. Inclusion and Exclusion Criteria

This section presents the search strategy for materials, Criteria for inclusion and exclusion, data extraction and ethical considerations for the review. This review was conducted according to the preferred reporting items fora systematic review [45].

3.2. Search Strategy

To find the desired literature, a comprehensive search was conducted for the period between 1st January 2015 and 30th October 2022. The databases searched included Ovid, Pubmed, Science Direct, Embase, Web of Science,AJOL, MEDLINE, CINAHL, Google Scholar and the search terms used included : 'Retinopathy'[MESH] OR 'retinopathy'[tiab] OR 'Prematurity[Mesh] OR 'prematurity'[tiab] OR 'retinopathy of prematurity'[tiab]

OR 'Deep learning'[MESH] OR 'deep learning for ROP disease diagnosis' [tiab] OR 'screening'[tiab] OR 'retinopathy screening guidelines'[tiab] OR ROP'[tiab] OR ' ROP screening'[tiab], 'Guideline'[tiab] OR 'Preterm'[tiab], 'classification'[tiab] OR 'Pathogenesis'[tiab] OR 'Sub- Saharan Africa'[tiab] OR 'global'[tiab]), 'rop statistics'[tiab] OR 'birth weight'[tiab] OR 'gestational period'[tiab].

Articles published in English and between 1st January 2015 and 30th October 2022 were included in this review, specifically original research papers, research dissertations and review papers on ROP screening and prevalence. Articles published in other languages were excluded, articles whose data collection was done before 1st January 2015, congress papers or posters, duplicate studies, studies which did not publish the years when data was collected.

3.3. Study Selection

A total of two hundred and thirty-eight (238) articles were identified. One hundred and fifty (152) were duplicates, the remaining eighty-six (86) were screened for inclusion based on the date when data had been collected and thirty (30) were excluded. Further screening was done, four (4) were excluded because they lacked ROP case percentages, six (6) studies were excluded because they lacked ROP screening guidelines and one (1) more English. All authors agreed on the inclusion of forty-five (45) studies in the final review as shown by Figure 3 for the PRISMA diagram [45].

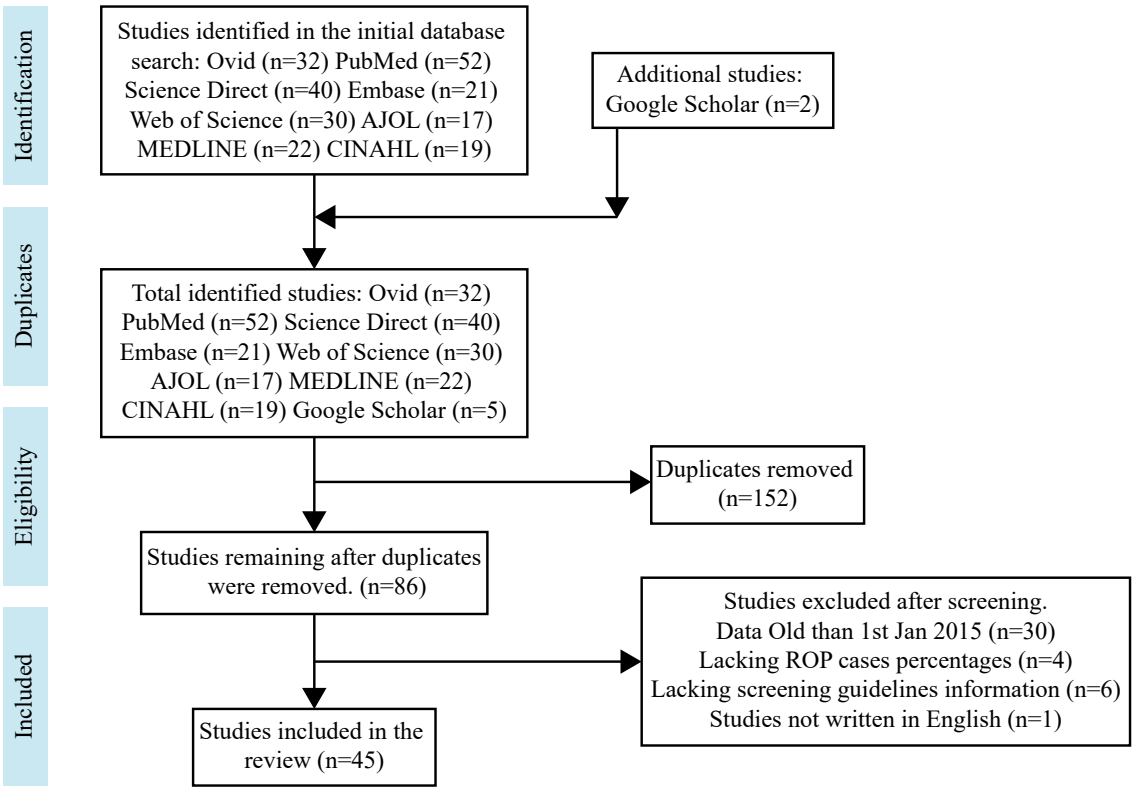

Figure 3: PRISMA Flow Diagram.

3.4. Data Extraction

A form was prepared and shared with all authors for review. Data was extracted and filled on the standard form which included details of name of the first author, year of publication, Year when the data was collected, The owner of the dataset, data size, ROP percentages, Birth weight, Gestation period and preterm rate. The authors extracted the data independently and any identified discrepancies were resolved through discussions and consensus. Duplicate references were checked and removed.

3.5. Ethical Considerations

This study was approved by Strathmore University Institutional Scientific and Ethical Review Committee (SUSERC), Certificate number (SU-ISERC1534/22) and approved by the Kenya National Commission for Science, Technology and Innovation (NACOSTI), license number (NACOSTI/P/23/23702). We do confirm that this work did not involve direct participation of human subjects or animals.

4. Results

As shown by Figure 4, in the United States, ROP incidents were 15% for a population of 717,277 [13]. In South Korea, for a population of 141,964, ROP cases were at 29.8% [14]. In Turkey, for dataset of 6,115, ROP cases were 27% [15]. In Canada, for a data set of 623, ROP cases were 67.1% [16]. In Brazil, for a dataset of 288, ROP cases were 26.4% [17]. In India, for dataset

of 157 infants, ROP cases were 11% [19] and a dataset of 211 ROP cases were at 21.8% [26]. In Argentina, a study done by Alda *et al.* [20] with a dataset of 2,739 showed that ROP cases were at 22.7%. In Russia, out of a dataset of 132, ROP cases were at 71.97% [21]. For China, a dataset of 4,069, ROP cases were at 17.9% [22]. In Japan, dataset of 692, ROP cases were at 77.6% [23]. In Turkey, a dataset of 2,186, ROP cases were 43.5% [24]. In the Netherlands, a dataset of 1,492, ROP cases were 20.4% [25].

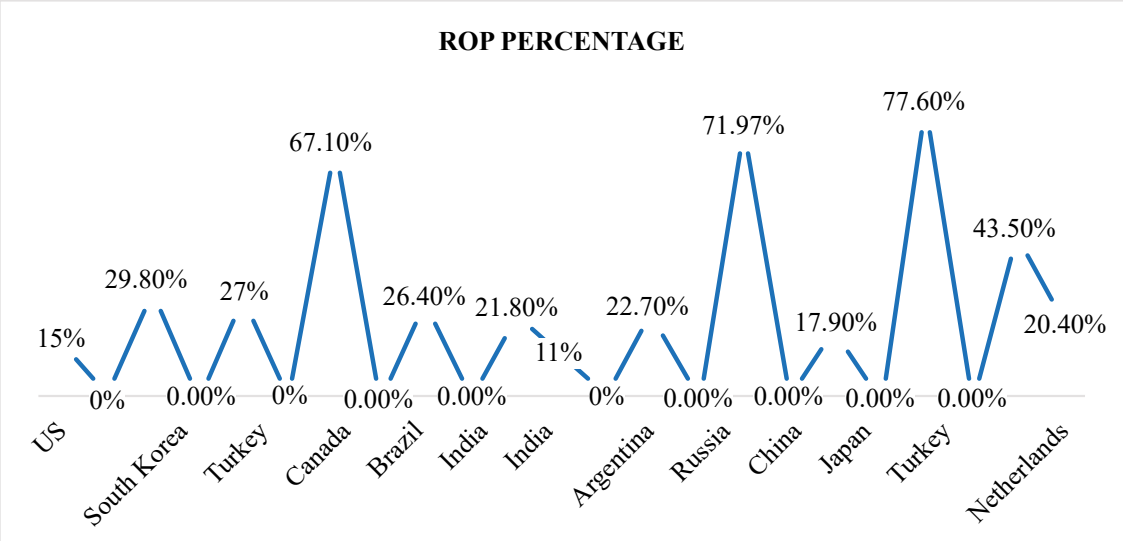

Figure 4: ROP Percentages Summary for Non-african Countries.

The ROP cases in Africa seem to be high but with few recent studies being published on the same. As shown by Figure 5, In Nigeria, a population of 723, ROP cases were at 17.6%. In Ethiopia [28], for a population of 66 infants, ROP cases were 42.4%. Egypt ROP cases were at 34.1% for a population of 240, [29]. In Ghana, a study population of 401, ROP cases were 13.7%, [30]. A study done by Seobi *et al.* [31] in South Africa for a population of 1,081 infants, ROP cases were at 24.3%. In Kenya, ROP cases were at 41.7% for a dataset of 163, [10]. A dataset of 5,640 infants collected from three hospitals in Cameroon showed that ROP cases were 14.8% [32]. In Rwanda, data collected from three hospitals and of size 424 infants, ROP cases were 7.3 [33].

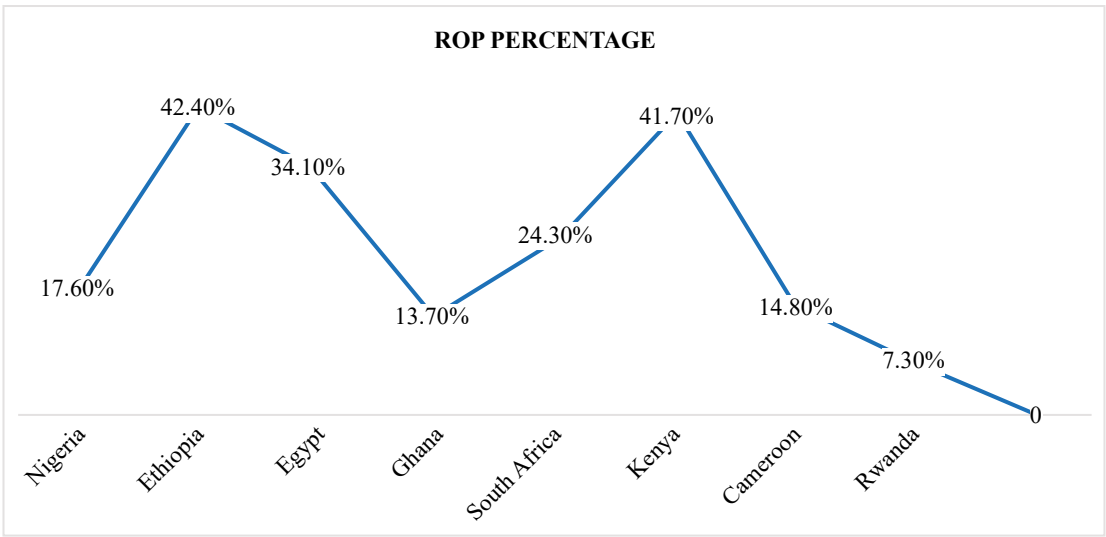

Figure 5: ROP Percentages Summary for Non-African Countries.

Preterm births summaries for African countries are shown in Figure 6. For Nigeria, out of a dataset of 1,129 the percentage was 32.9% [35], For Ethiopia, out of a dataset of 482, the preterm birth percentage was 11.4% [36], In Egypt for a dataset of 250, the preterm percentage was 28% [37]. In Ghana, for a population of 680, preterm births were 14.1% [38]. In South Africa, for a population of 760, preterm births

were at 16.4% [39]. A cross sectional study done by Waiswa *et al.* [40] to determine the preterm births between Kenya and Uganda, for a population of 16,966 and 34,015, the preterm births percentages were 12.6% and 13.4% respectively. In Cameroon, for a population of 38,151, the preterm births were 14.8%, [32] and for Rwanda the preterm births were 10% for a population of 363,000 [35].

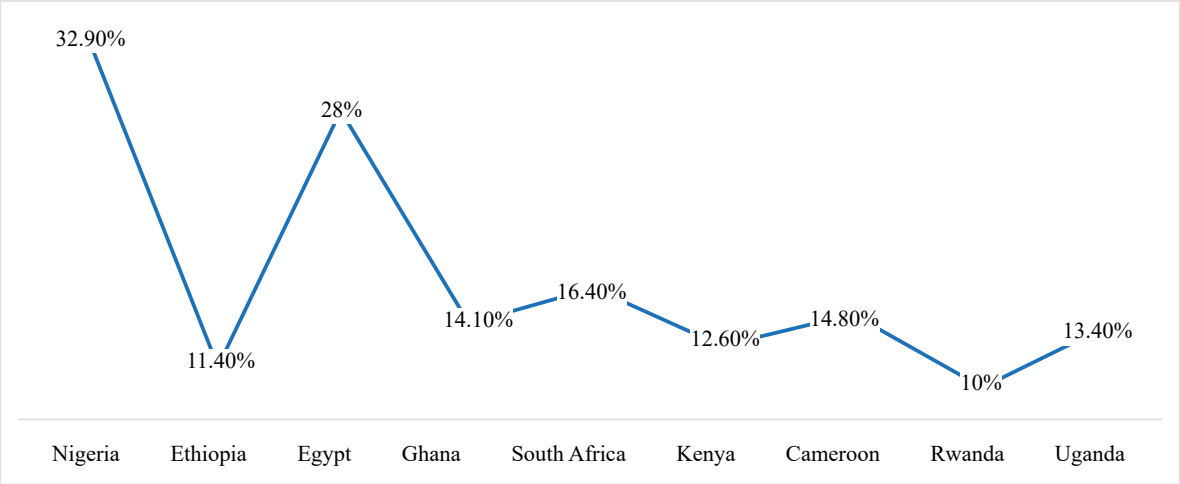

Figure 6: ROP Preterm Births Percentages Within African Countries.

4.1. Conclusion

This paper presents a systematic review of the pathogenesis of Retinopathy of Prematurity disease as well as the zones in which the disease can be found and the disease stages. A procedure for the disease diagnosis is also presented. ROP disease has no symptoms hence early diagnosis of the disease is important. Stage 1 and 2 of ROP can heal without any medical intervention but diagnosis at stage 3 is important to stop its progression to stage 4. From this study, we can conclude that babies born preterm need to be screened for Retinopathy of Prematurity. South Africa and Kenya are the only countries in Africa with national ROP screening guidelines despite the disease being one of the leading causes of blindness world-wide. Some of the challenges associated with the disease diagnosis include few ophthalmologists to assist in screening and the disease diagnosis, lack of equipment's at most of the hospitals in Africa, improper lighting during image capturing which may result to the disease stage misdiagnosis. Low birth weight and low gestational age are key factors for ROP screening and can be considered as key requirements during screening by countries without screening guidelines. The many countries within Africa with no screening guidelines can study the South Africa and Kenyan guidelines and establish their screening guidelines. From this work, it is observed that there are few studies published about ROP disease cases whose data was collected from the period 2018 to 2022. Deep Learning applications have widely been developed to diagnose Retinopathy of Prematurity (ROP). Despite the advancements, there are still challenges to be addressed. Some of the challenges include:

Device inconsistency and low-quality images: Some databases contain both colored and non- colored images. Image resolution and clarity vary both from colored to non-colored images and this may result in an increase in the prediction errors. There are many different cameras used to capture retina images. Device inconsistency produces images with different orientation, size, and resolution.

Model training: Deep Learning models require huge data sets for training the models to achieve better results. To address this challenge, three methods are proposed: First, Transfer Learning can be used. This method allows usage of data collected from similar projects where this method helps to enhance the original input representations of data and for mapping the data. The second approach which can be used is customizing an existing similar model and changing some layers and fine tuning some parameters. This is useful, since the model being customized is already trained with enough dataset(s) and images are already resized, so not much additional work is required for data preparation. However, this method is limited in the fact that not every model should be customized, especially for bioinformatics solutions. The third approach is applying some simulations to increase data volumes. Simulators can be developed to simulate the number of required images. However, it should be noted that not every problem will use simulators for data generation.

Imbalanced data: Data in many databases are always imbalanced with some sets being more or lesser than the others. Training a Deep Learning model with imbalanced data will result in inaccurate results. The following two techniques can be used to solve this problem. First, developers require to utilize the correct criteria for evaluating the model loss and prediction result functions. For example, the model can employ area under curve (AUC) to show the resultant model

loss. Another solution to this problem is to utilize the weighted cross entropy loss function. This allows the model to produce good results with small classes through enabling the model to up-sample small classes or down- sample large classes.

Acknowledgments: This work was supported by DAAD, Organization for Women in Science for the Developing World (OWSD) and Google PhD Research.

Disclosures: The authors report no conflicts of interests.

■ Reference

1. **Sabri K, Ells AL, Lee EY, Dutta S, Vinekar A**. Retinopathy of prematurity: a global perspective and recent developments. *Pediatrics* 2022. 150(3).
2. **Tsai ASH, Acaba-Berrocal L, Sobhy M, Cole E, Ostmo S, Jonas K, et al.** Current Management of Retinopathy of Prematurity. *Current Treatment Options in Pediatrics* 2022. 8(3):246-61.
3. **Tiryaki Demir S, Karapapak M, Uslu HS, Bulbul A, Guven D, Dirim AB, et al.** Retinopathy screening results of late-preterm infants born at 32–35 weeks of gestational age. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2019. 257(6):1325-9.
4. **Chan-Ling T, Gole GA, Quinn GE, Adamson SJ, Darlow BA**. Pathophysiology, screening and treatment of ROP: A multi-disciplinary perspective. *Progress in Retinal and Eye Research* 2018. 62:77-119.
5. **Agarwal K, Jalali S**. Classification of retinopathy of prematurity: from then till now. *Community Eye Health* 2017. 30(99):S4-s7.
6. **Xu S, Liang Z, Du Q, Li Z, Tan G, Nie C, et al.** A systematic study on the prevention and treatment of retinopathy of prematurity in China. *BMC Ophthalmology* 2018. 18(1):44.
7. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. *Arch Ophthalmol* 1984. 102(8):1130-4.
8. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005. 123(7):991-9.
9. **Molinari A, Weaver D, Jalali S**. Classifying retinopathy of prematurity. *Community Eye Health* 2017. 30(99):55-6.
10. **Onyango O, Sitati S, Amolo L, Murila F, Wariua S, Nyamu G, et al.** Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. *Pan African Medical Journal* 2018. 29(1):1-7.
11. **Tsai ASH, Chou H-D, Ling XC, Al-Khaled T, Valikodath N, Cole E, et al.** Assessment and management of retinopathy of prematurity in the era of anti-vascular endothelial growth factor (VEGF). *Progress in Retinal and Eye Research* 2022. 88:101018.
12. **Hellström A, Ley D, Hansen-Pupp I, Hallberg B, Ramenghi LA, Löfqvist C, et al.** IGF-I in the clinics: Use in retinopathy of prematurity. *Growth Hormone & IGF Research* 2016. 30-31:75-80.
13. **Thangamathesvaran L, Wang J, Repka MX, Scott AW**. Trends in Retinopathy of Prematurity Care in the United States 2009–2018: A Nationwide Analysis Using National Inpatient Sample. *Ophthalmology Retina* 2023. 7(4):360-6.
14. **Hong EH, Shin YU, Bae GH, Choi YJ, Ahn SJ, Sobrin L, et al.** Nationwide incidence and treatment pattern of retinopathy of prematurity in South Korea using the 2007–2018 national health insurance claims data. *Scientific Reports* 2021. 11(1):1451.
15. **Bas AY, Demirel N, Koc E, Isik DU, Hirfanoglu İM, Tunc T**. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *British journal of ophthalmology* 2018. 102(12):1711-6.
16. **Isaza G, Donaldson L, Chaudhary V**. Increased incidence of retinopathy of prematurity and evolving treatment modalities at a Canadian tertiary centre. *Canadian Journal of Ophthalmology* 2019. 54(2):269-74.
17. **Martins TGdS, Andreghetto LdAF, Brito RM, Provenzano LB, Fowler S**. Evaluation of the prematurity retinopathy and other eye changes in the newborn. *einstein (São Paulo)* 2022. 20:eAO6692.
18. **Sanghi G, Sawhney JS, Kaur S, Kumar N**. Evaluation of clinical profile and screening guidelines of retinopathy of prematurity in an urban level III neonatal intensive care unit. *Indian J Ophthalmol* 2022. 70(7):2476-9.
19. **Sabherwal S, Gilbert C, Foster A, Kumar P**. ROP screening and treatment in four district-level special newborn care units in India: a cross-sectional study of screening and treatment rates. *BMJ Paediatr Open* 2021. 5(1):e000930.
20. **Alda E, Lomuto CC, Benítez AM, Bouzas L, Brussa M, Cattaino A, et al.** Results of the National Program for the Prevention of Blindness in Childhood by Retinopathy of Prematurity in Argentina (2004-2016). *Arch Argent Pediatr* 2018. 116(6):386-93.
21. **Sidorenko E**. Treatment of retinopathy of prematurity with aflibercept in Russia. *17th Int Conf Clin Exp Ophthalmol* 2018.1-3.
22. **Li L, Gao Y, Chen W, Han M**. Screening for retinopathy of prematurity in North China. *BMC Ophthalmology* 2022. 22(1):251.
23. **Shiraki A, Fukushima Y, Kawasaki R, Sakaguchi H, Mitsuhashi M, Ineyama H, et al.** Retrospective Validation of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Criteria in a Japanese Cohort. *American Journal of Ophthalmology* 2019. 205:50-3.
24. **Yucel OE, Eraydin B, Niyaz L, Terzi O**. Incidence and risk factors for retinopathy of prematurity in premature, extremely low birth weight and

extremely low gestational age infants. *BMC Ophthalmology* 2022. 22(1):367.

25. **Trzcionkowska K, Termote JU, Böhringer S, van Sorge AJ, Schalij-Delfos N**. Nationwide inventory on retinopathy of prematurity screening in the Netherlands. *British Journal of Ophthalmology* 2023. 107(5):712-6.
26. **Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al.** The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery* 2021. 88:105906.
27. **Ademola-Popoola DS, Fajolu IB, Gilbert C, Olusanya BA, Onakpoya OH, Ezisi CN, et al.** Strengthening retinopathy of prematurity screening and treatment services in Nigeria: a case study of activities, challenges and outcomes 2017-2020. *BMJ open ophthalmology* 2021. 6(1):e000645.
28. **Melesse MA**. Retinopathy of prematurity-an emerging cause of childhood blindness in Ethiopia. *Ethiopian Medical Journal* 2020. 58(02).
29. **Noor MS, Elbarbary M, Embabi SN, Zaki MA, Awad H, Al-Feky M**. Screening and Risk Factors for Retinopathy of Prematurity in a Tertiary Care Hospital in Cairo, Egypt. *Clin Ophthalmol* 2022. 16:3257-67.
30. **Braimah IZ, Enweronu-Laryea C, Sackey AH, Kenu E, Agyabeng K, Ofori-Adjei I-OD-B, et al.** Incidence and risk factors of retinopathy of prematurity in Korle-Bu Teaching Hospital: a baseline prospective study. *BMJ open* 2020. 10(8):e035341.
31. **Seobi T, Maposa I, Makgotloe MA**. Retinopathy of prematurity screening in Johannesburg, South Africa: A comparative study. *African Vision and Eye Health* 2022. 81(1):5.
32. **Epee Ngoue J, Essiben F, Sap SNU, Meka E, Nga Motaze A, Ntsama P, et al.** Epidemiology of Preterm Birth Over a 5-Year Period in Yaoundé (Cameroon). *Global Pediatric Health* 2022. 9:2333794X221074319.
33. **Mutangana F, Muhizi C, Mudereva G, Noë P, Musiime S, Ngambe T, et al.** Retinopathy of prematurity in Rwanda: a prospective multi-centre study following introduction of screening and treatment services. *Eye* 2020. 34(5):847-56.
34. **Adugna DG**. Prevalence and associated risk factors of preterm birth among neonates in referral hospitals of Amhara Region, Ethiopia. *Plos one* 2022. 17(10):e0276793.
35. **Every Preemie—SCALE.** Rwanda: Profile of Preterm and Low Birth Weight Prevention and Care. 2017. Available from: http://www.everypreemie.org/wp-content/uploads/2016/02/Rwanda.pdf.
36. **Mustapha B, Simon P, Abdullahi B, Abubakar H**. Prevalence and associated morbidities of preterm neonatal admissions at the University of Maiduguri Teaching Hospital, North-Eastern Nigeria. *Nigerian Journal of Paediatrics* 2020. 47(3):264–9-–9.
37. **Algameel A, Elhawary M, Amin S, Abd Elmenem M**. Outcome of late preterm newborns in Upper Egypt. *Egyptian Pediatric Association Gazette* 2020. 68(1):11.
38. **Axame WK, Binka FN, Kweku M**. Prevalence and factors associated with low birth weight and preterm delivery in the ho municipality of Ghana. *Advances in Public Health* 2022. 2022:1-11.
39. **Jeena PM, Asharam K, Mitku AA, Naidoo P, Naidoo RN**. Maternal demographic and antenatal factors, low birth weight and preterm birth: findings from the mother and child in the environment (MACE) birth cohort, Durban, South Africa. *BMC Pregnancy and Childbirth* 2020. 20(1):628.
40. **Waiswa P, Higgins BV, Mubiri P, Kirumbi L, Butrick E, Merai R, et al.** Pregnancy outcomes in facility deliveries in Kenya and Uganda: A large cross-sectional analysis of maternity registers illuminating opportunities for mortality prevention. *Plos one* 2020. 15(6):e0233845.
41. **Mwangi N, Onyango O, Gachago M, Murila F, Njambi L, Gichangi M, et al.** National guidelines for Screening and Management of Retinopathy of Prematurity in Kenya. Ministry of Health, Nairobi; 2018.
42. **Blease C, Kaptchuk TJ, Bernstein MH, Mandl KD, Halamka JD, DesRoches CM**. Artificial intelligence and the future of primary care: exploratory qualitative study of UK general practitioners' views. *Journal of medical Internet research* 2019. 21(3):e12802.
43. **Smith H, Fotheringham K**. Artificial intelligence in clinical decision-making: Rethinking liability. *Medical Law International* 2020. 20(2):131-54.
44. **Liu X, Faes L, Kale AU, Wagner SK, Fu DJ, Bruynseels A, et al.** A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *The lancet digital health* 2019. 1(6):e271-e97.
45. **Wang D, Duke R, Chan RP, Campbell JP**. Retinopathy of prematurity in Africa: a systematic review. *Ophthalmic Epidemiology* 2019. 26(4):223-30.