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Agrawal, Ranjana; Agrawal, Manasi Anup; Kulkarni, Sucheta; Kotecha, Ketan; and Walambe, Rahee, "Quantitative analysis of research on Artificial Intelligence in Retinopathy of Prematurity" (2021). *Library Philosophy and Practice (e-journal)*. 5342. https://digitalcommons.unl.edu/libphilprac/5342

# Quantitative analysis of research on Artificial Intelligence in Retinopathy of Prematurity

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### Abstract

Retinopathy of Prematurity (ROP) is a disease of the eye and a potential source of blindness in low birth weight preterm infants. It is preventable if diagnosed and treated on time. Artificial Intelligence (AI) has played an important role in developing automated screening systems to assist medical experts. There are many traditional literature review articles available that focus on the scientific content of ROP-AI. The researchers also require a bibliometric analysis to become acquainted with the competing groups and new trends in this field. This paper gives a brief overview of ROP and AI systems for ROP screening with a statistical analysis of the Scopus database's related documents.

**Keywords**: retinopathy of prematurity, deep learning, machine learning, automated, artificial intelligence, bibliometric survey

### Introduction

Retinopathy of Prematurity (ROP) is an eye disease incurred by irregular retinal vessel growth in the retina and is a potential cause of blindness. The normal fundus image with optic disc, macula, and vessels is shown in Figure 1. ROP is usually observed in premature infants weighing less than 2000 grams and having a less than 34 weeks gestation age. The ROP specialists describe ROP by its location, severity, and appearance of enlarged & tortuous retinal vessels (plus disease). Depending upon its location and severity, ROP has been classified into five stages and three zones (ICROP 2005).

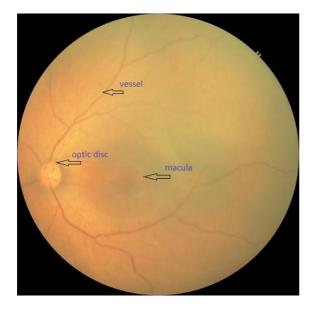


Figure 1. Fundus Image

Stages I-V of ROP shown in Figure 2 and Figure 3 determine the disease's severity. The different stages are described as:

- Stage I: A demarcation line separating the avascular & vascular retina indicates the presence of Stage I.
- Stage II: The demarcation line becomes thick and wide and gets converted to a ridge.
- Stage III: is observed when blood vessels grow abnormally.
- Stage IV: Partial retinal detachment. The abnormal blood vessels start bleeding, causing the tissue to scar.
- Stage V: Total retinal detachment. It is the last stage of ROP, and if left untreated, it can cause irreversible vision loss. The dilated and tortuous vessels of the retina indicate plus disease

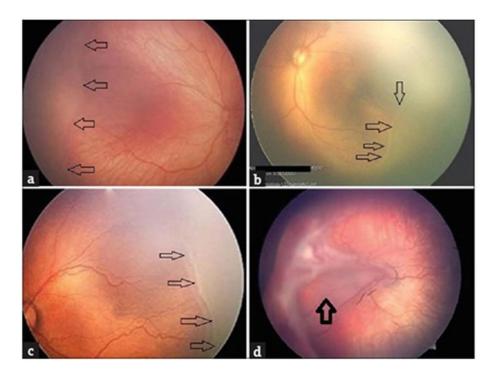


Figure 2(a) Stage I, Figure 2(b) Stage II, Figure 2(c) Stage III, Figure 2(d) Stage IV (Source:<u>https://www.jcnonweb.com/</u>)

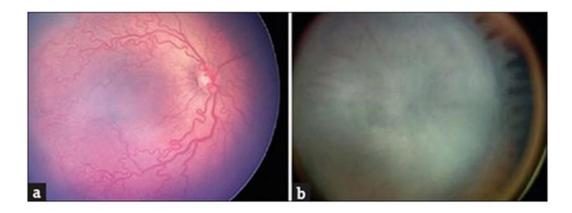


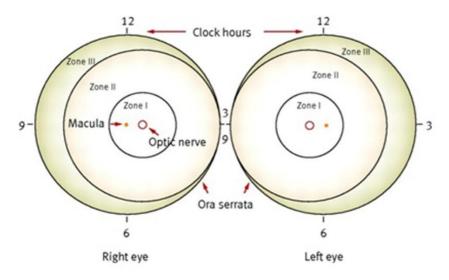
Figure 3(a) Plus Disease, Figure 3(b) ROP Stage V

(Source:<u>https://www.jcnonweb.com</u>/)

Additionally, zones are defined as shown in Figure 4.

• Zone I is a circular area around the optic disc. Its radius is equivalent to double the distance between the macula and the optic disc.

• On the nasal side, the circle extending to the ora serrata is Zone II



• Zone III is beyond Zone II seen in the temporal retina.

Figure 4. ROP Zones (Source: <u>https://www.bmj.com</u>)

Most of the time, ROP regresses spontaneously on its own, causing no damage to the baby's eyes. Infants with Stage I and II have higher chances of full recovery without any treatment and vision damage. But the advanced stages (stage IV and V) of ROP can cause serious vision problems such as dragging of the retina, bleeding inside the eye, cataracts, or permanent loss of vision in the infants. Aggressive posterior retinopathy of prematurity (APROP) is a severe ROP form (Figure 5) that progresses to retinal detachment if not treated urgently (Bellsmith et al. 2020). ROP is treated with laser therapy or cryotherapy to slow abnormal blood vessel growth when the disease is in stage III. In the most severe ROP stages, eye surgery may be required.

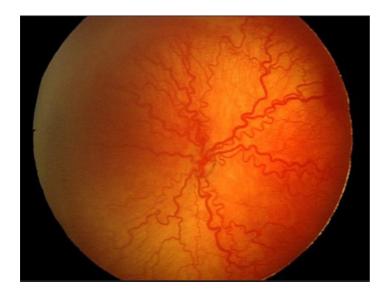


Figure 5. APROP (Source: https://www.futurelearn.com)

ROP can be identified through timely screening, which is performed using special equipment like a Retcam/Neo camera by the ophthalmologists. Current challenges in screening program are: 1) Number of infants who need ROP screening are ROP exceedingly high compared to ROP specialists available. 2) There can be subjective variability in diagnosis even among the experts'. 3) Most specialists are placed in urban regions and are not accessible to at-risk infants from smaller towns, rural areas. Automated screening systems using AI are developed to resolve these issues and assist the medical experts. It will reduce the time of ophthalmologists in diagnosis so that they can concentrate on critical cases. The infants can be referred for treatment on time with the efficient screening done by an automatic system preventing blindness. A telemedicine screening model is used in rural areas of low and middle-income countries where ROP specialists are not available for screening. The fundus images are captured and graded by trained non-physician technicians in the NICU (Vinekar et al. 2014) or are sent to a remote location for an ophthalmologist evaluation (Shah et al. 2018; Antaki et al. 2020; Greenwald et al. 2020; Brady et al. 2020; Li et al. 2020; Bao et al. 2021). Smartphone imaging used for telemedicine can also minimize imaging costs in lowincome territories (Wintergerst et al. 2020).

Artificial Intelligence is used widely to detect many ophthalmology diseases, such as glaucoma, Diabetic Retinopathy, ROP, AMD (age-related macular degeneration) (Ting et al. 2019; Gensure et al. 2020, Dutt et al. 2020; Perepelkina and Fulton 2021). Machine Learning (ML) algorithms were applied to diagnose pediatric cataracts, strabismus, refractive error, reading disability, future high myopia (Sivakumar et al. 2016; Rani et al. 2016; Reid and Eaton 2019; Oke and VanderVeen 2021). These techniques were time-consuming and not accurate for complex problems. With advancements in hardware and technology, Deep Learning(DL) is gaining popularity in clinical ophthalmology (Goldhaegon et al. 2020).

Image analysis applications in the automated diagnosis of diabetic retinopathy and telemedicine are studied (Patton et al. 2006). Plus, disease diagnosis agreement among the ROP specialists required to implement computer-aided ROP systems and telemedicine was measured (Chiang et al. 2007). Vessel width and tortuosity visible in fundus images were measured using the semiautomatic method (Wilson et al. 2008). Assessment of semiautomatic tools such as ROPtool, Retinal Image Multiscale Analysis (RISA) was performed to determine plus disease. It was concluded that a computerbased system could reduce subjective variability in detecting plus disease (Wallace 2007; Koreen et al. 2007; Vickers et al. 2015). Severe ROP was predicted by longitudinal postnatal weight gain using the WINROP tool. It is validated for a US group (Wu et al. 2010; Choi et al. 2013). APROP can be detected automatically by ML algorithms and segmentation of the vessels (Woo et al. 2015).

The first automated system using convolution Neural Networks (CNN) was developed to detect ROP (Worrall et al. 2016). Normal, pre–plus ROP disease were identified automatically (Brown et al. 2018) by a deep learning network with U-Net architecture. A deep neural networks-based method (DeepROP) was developed to detect the presence of ROP and its severity (Wang et al. 2018). A fully convolutional network with multi-instance learning was used to detect ROP stages (Chen et al. 2019; Mulay et al. 2019; DIng et al. 2020). A system using two deep convolution networks was proposed to identify ROP's existence and classify it into Regular ROP or APROP (Zhang et al. 2019). A Hierarchical Bilinear Pooling with Squeeze and Excitation network was used to detect APROP (Zhang et al. 2020). Transfer learning using deep neural network architectures was used to identify ROP and its severity of the disease (Huang et al. 2020).

The automated system for classifying normal,stage2, and stage 3 images was developed for telemedicine screening (Vijayalakshmi et al. 2020). Plus disease was detected from the vessel's width, tortuosity, density, and fractal dimension using a deep learning network (Mao et al. 2020). Network-based architectures were proposed for vascular structure segmentation in medical images (Islam and Indiramma 2020). ROP images have low contrast; An automated method was developed to improve the retinal vessels' visibility (Intriago-Pazmino et al. 2020). Zone I was detected by a deep learning framework from RetCam images having both optic disc and macula (Zhao et al. 2019). We developed a method to detect Zone I, II, and III in the posterior view of fundus images of infants (Agrawal, forthcoming). Computer-aided systems were developed using ML and DL, but they are not used clinically in ophthalmology because of the challenges like AI as a black box, generalizability, and medicolegal issues (Ting et al. 2019; Scruggs et al. 2020).

### **Bibliometric analysis of ROP**

A thorough bibliometric study is explained in this section with the documents retrieved over 20 years from 2000 to 2021. This study aims to understand the role of AI in ROP, the work done so far, and future scope in this field. There are several methods and databases available to retrieve the data for the bibliometric analysis. Some of the approved publication databases are Web of Science, Scopus, ScienceDirect, Clarivate, Google Scholar, SCImago, Mendeley, Research Gate, etc. Scopus is the largest database of peer-reviewed research literature in science, engineering, technology, and medicine (Chaudhary and Mulay 2019; Dixit et al. 2020).

We searched the Scopus database with the phrase of the following keywords: KEY (Retinopathy AND of AND prematurity) AND ABS (Deep AND Learning ) OR ABS (Computer ) OR ABS (Machine AND learning ) OR ABS (Automated) OR ABS (Artificial Intelligence)). Preliminary investigation through this phrase generated 192 publications. It was then scrutinized to 143 subjectrelevant papers by applying year and language filters. The distribution of the documents by their type is shown in Figure 6. Out of 143 publications, 84 are from journals(5 articles are yet to be published), 36 are conference papers with 22 review papers and one book chapter.

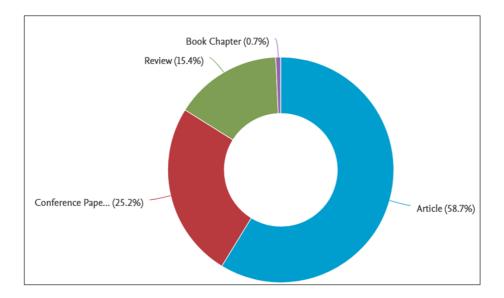


Figure 6. . Distribution of documents by their type (Source: <u>http://www.scopus.com</u> accessed on 10Apr2021)

The yearly trend of publications is illustrated in Figure 7. Artificial intelligence in medical imaging was highlighted around the year 2016 with the invention of Deep Learning. The development of automated systems in ROP using Deep Learning was started recently, in 2018. The first automatic screening system was developed in 2016. There are only 14, 25, and 33 publications on ROP in 2018, 2019, 2020, respectively. It includes review papers, automated systems for detecting ROP, Plus disease detection, APROP detection, and Telemedicine. The number of publications is comparatively less, indicating extensive future scope in the research in ROP.

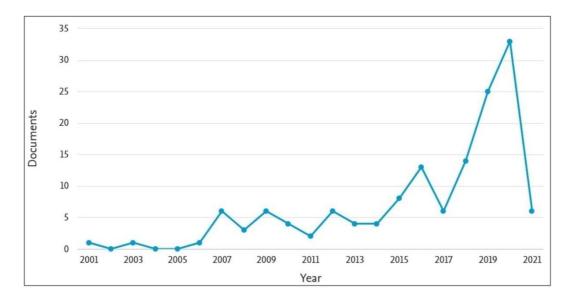
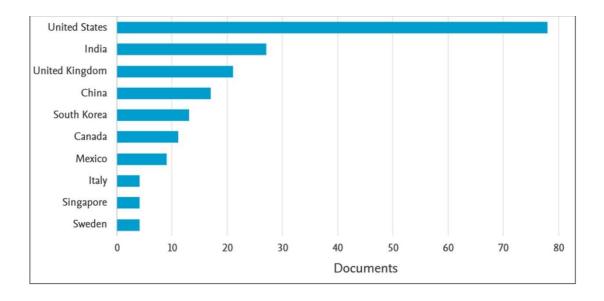


Figure 7. The yearly trend of publications (Source: <u>http://www.scopus.com</u> accessed on 10Apr2021)

Figure 8 shows the bar chart of country-wise research contribution in ROP. A total of 30 countries have enriched the ROP-AI research in the past 20 years. The United States is dominant with 78 publications, followed by India with 27 papers. Research work on telemedicine is being conducted to cover the rural areas in India. The United Kingdom and China have 21 and 17 publications, followed by other countries' publications, as shown in Table 1.



## Figure 8. Bar chart of country-wise research contribution

(Source:<u>http://www.scopus.com</u>)

	Number of	~	Number of		
Country	publications	Country	publications		
United States	78	Germany	2		
India	27	Austria	2		
United Kingdom	21	Hong Kong	2		
China	17	Israel	2		
South Korea	13	Netherlands	2		
Canada	11	Qatar	2		
Mexico	9	Brazil	1		
Italy	4	Chile	1		
Singapore	4	Ecuador	1		
Sweden	4	Finland	1		
Australia	3	Iran	1		
Japan	3	Malaysia	1		
Spain	3	New Zealand	1		

### Table 1. Country-wise Publication list

Taiwan	3	Pakistan	1
Turkey	3	Switzerland	1

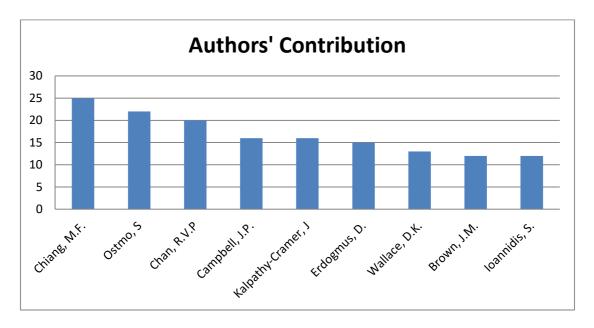


Figure 9. Authors' contribution graph

A summary of the top ten authors' contributions in the ROP-AI research is given in Figure 9. Out of 160 researchers, Chiang, M.F. has a maximum number of publications, 25, followed by Ostmo, S., with 22 and Chan, R.V.P. with 20 papers.

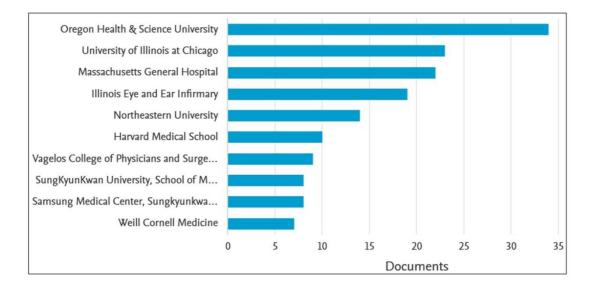


Figure 10. Affiliation graph

The affiliation statistics of the pre-eminent ten universities in ROP research are as shown in Figure 10. The Oregon Health and Science University published 34 articles, the University of Illinois at Chicago has 23 publications on its name, and Massachusettes General Hospital has 22 papers.

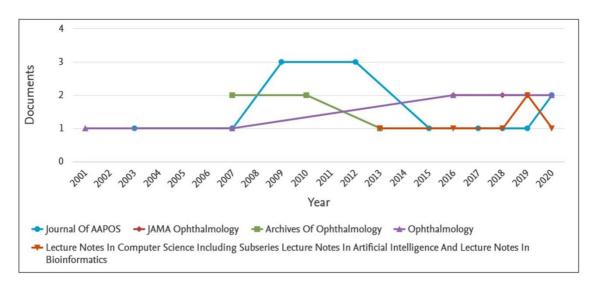


Figure 11. Count of documents published per year by pre-eminent five journals

Figure 11 and Table 2 depict the quantitative analysis of documents published per year in the pre-eminent five journals. As the research field topics of ROP are multidisciplinary, they are published in over 61 different journals. At the pinnacle are journals related to medicine, i.e., ophthalmology. Journal of AAPOS having SCImago Journal Rank (SJR:0.748) has the highest publications, 14. JAMA ophthalmology (SJR:2.729), Lecture Notes in Computer Science (SJR:0.427), and ophthalmology (SJR:4.414) each contain six papers. Archives of Ophthalmology, Progress In Biomedical Optics And Imaging Proceedings Of SPIE, and Translational Vision Science And Technology have five publications.

Table 2.	Source	Statistics
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Source	Number of Documents
Journal of AAPOS	14
JAMA Ophthalmology	6
Lecture Notes in Computer Science Including	
Subseries Lecture Notes in Artificial Intelligence and	6
Lecture Notes in Bioinformatics	
Ophthalmology	6
Archives of Ophthalmology	5
Progress in Biomedical Optics and Image	5
Proceedings of SPIE	
Translational Vision Science and Technology	5
Current Opinion in Ophthalmology	4

The number of citations per year for Artificial Intelligence in Retinopathy of prematurity is illustrated in Figures 12 and Table 3. The selected 143 papers have been cited 2569 times to date. In the past five years, the citation count of these papers is

around 1427, with the year 2020 having the maximum number of citations at 563. The subsequent table depicts a list of the top 12 articles cited the most times.

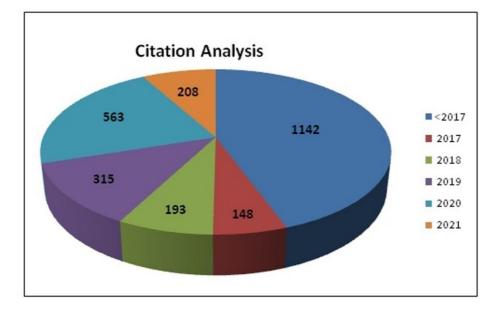


Figure 12. Number of citations for the documents

Publication Title	< 2017	2017	2018	2019	2020	2021	Total
Retinal image analysis:							
Concepts, applications and	329	31	34	28	24	8	454
potential							
Interexpert agreement of plus							
disease diagnosis in	116	12	16	16	19	5	184
retinopathy of prematurity							
Artificial intelligence and							
deep learning in	-	-	-	29	97	38	164
ophthalmology							
Computerized analysis of	106	6	6	9	8	1	136

Table 3.	Citation	Analysis
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retinal vessel width and							
tortuosity in premature infants							
Automated diagnosis of plus							
disease in Retinopathy of	_	_	6	44	62	19	131
prematurity using deep			0		02	17	101
convolutional neural networks							
Longitudinal postnatal weight							
measurements for the	57	10	8	7	14	3	99
prediction of Retinopathy of	57	10	0	/	14	5	<u> </u>
prematurity							
Computer-automated							
quantification of plus disease	54	3	2	4	4	-	67
in Retinopathy of prematurity							
Deep learning in							
ophthalmology: The technical	-	-	-	6	44	15	65
and clinical considerations							
Evaluation of a Computer-							
Based System for Plus	46	5	6	6	2	_	65
Disease Diagnosis in	40	5	0	0	2	-	05
Retinopathy of Prematurity							
Accuracy of ROPtool vs							
individual examiners in	49	4	2	1	3	2	61
assessing retinal vascular			-		5	-	01
tortuosity							
Plus disease in +Retinopathy	44	3	2	5	3	-	57

of prematurity: Pilot study of				
computer-based and expert				
diagnosis				

Figure 13 shows the percentage-wise distribution of ROP-AI documents in different subject areas. This distribution will help the researchers to select the appropriate journal. Medicine, computer science, and engineering cover 74.5% of subjects area as ROP is the medical subject and AI falls in computer science and engineering. Other topics like Neuroscience, Mathematics, Physics, and Biochemistry merely contribute to ROP research.

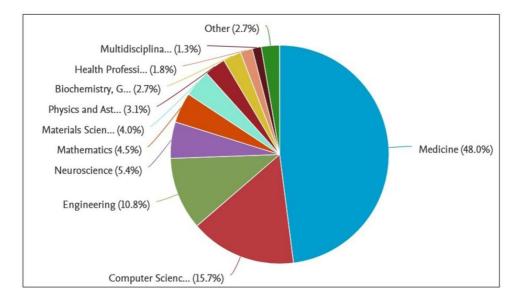


Figure 13. Percentage-wise distribution of documents in different subject areas

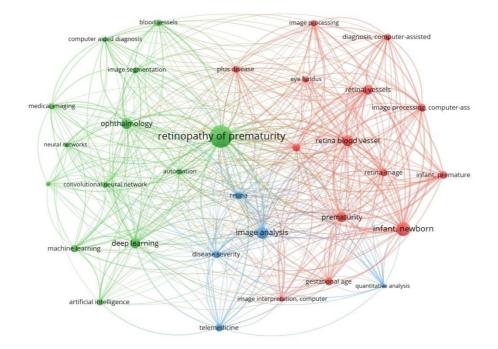


Figure 14. Network Map illustrating the interconnection of all keywords

Figure 14 is a network map obtained from the VOSviewer tool. It represents the interconnection between various keywords and document titles. The size of the solid colored circles is directly proportional to the number of occurrences of the keyword. For example, the circle of 'Retinopathy of Prematurity' keyword is the biggest, indicating that it has the highest count among all the keywords. The 'newborn' keyword has the second biggest circle, which implies the second-highest occurrence among all 143 sources. Keywords like ophthalmology, retinal blood vessel, image analysis have similar sizes showing nearly the same count.

The links between the two circles, shown in Figure 15, indicate the distance between them, i.e., the association between two keywords. The shorter the distance between two keywords, the stronger is the association. For example, plus disease and retina have shorter links to the keyword 'retinopathy of prematurity', showing a stronger bond between them. Hence, these visualizations depicted in Figure 14 and Figure 15 are

essential to understand the important keywords and their connection with other keywords.

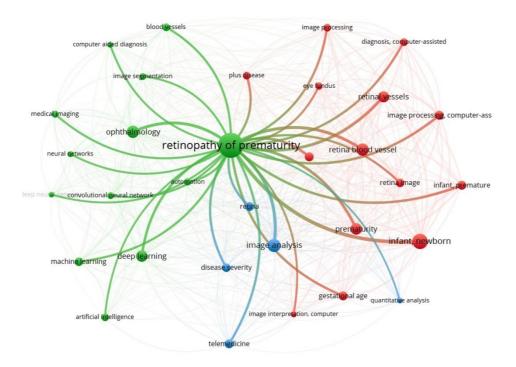


Figure 15. Network visualization map showing interlinkage between 'Retinopathy of Prematurity' keyword with other keywords

Retinopathy of Prematurity research aims to reduce blindness in children. As it has high social relevance, there are many funding sources available for ROP research, as shown in the bar graph of Fig 16. Five institutes sponsoring maximum research work are shown in fig with the counts. National Institutes of Health has the most fundings at 50, U.S. Department of Health and Human Services 45, National Eye Institute 32, Research to Prevent Blindness 30, and National Science Foundation 17 projects.

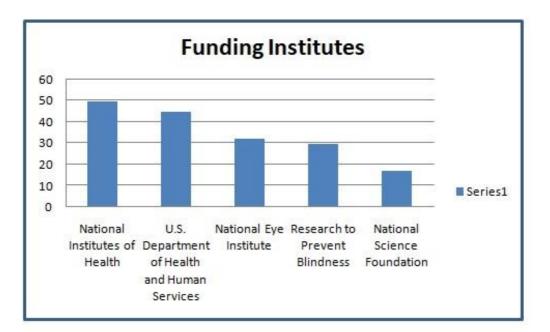


Figure 16. Bar graph of Funding Sources

### **Future Scope**

Artificial Intelligence is widely used for medical imaging. Retinopathy of Prematurity epidemic has begun because of neonatology developments. Due to the low patient-todoctor ratio in ROP and subjective variability in the diagnosis, automated systems are developed to assist the ophthalmologists in timely screening the infants. The major challenges in ROP research are the unavailability of annotated training data sets and the incomplete development of the vascular structure of the retina in premature infants.

This bibliometric study shows that there are only 143 Scopus papers in the past 20 years in ROP-AI research. We have manually segregated these papers into different categories as study/review papers, Automated systems for detecting ROP, Retinal vessel segmentation, Plus disease detection, ROP Stage detection, Aggressive Posterior Retinopathy of Prematurity(APROP) detection, and Telemedicine. It is observed that 63 papers are based on the study/review, and 80 articles are on automated systems. Out of these, there are only 4 and 8 publications for APROP and Telemedicine, respectively.

Retinal vessel segmentation is performed majorly on public datasets available for Diabetic Retinopathy as preparing the ground truths for segmentation is a complex work. It indicates there is a wide scope of research in this field exploring all characteristics of ROP.

### Conclusion

We have performed the quantitative analysis for ROP-AI publications drawn from the Scopus database. It will provide a basic guideline to the new researchers to learn the recent trends and help assess research and productivity. We have analyzed 143 Journal/Conference papers in the past 20 years, out of which 63 documents were found as study/review papers. The bibliometric analysis provides the documents count per year with journals, authors, subject areas, countries, and other details. The citation count and funding sources details make it easy for the researcher to decide the journals for work publication following the new trends. The survey reveals that the USA, India, UK, and China are dominant in ROP-AI research. Still, the automated systems developed for ROP screening face a few challenges to be implemented clinically. Indian researchers need to explore more automated systems as the disease burden of ROP is high in India, and ROP experts available are insufficient.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sec.

### **Conflicts of interest**

The authors declare that they have no conflict of interest.

#### Declaration

This study does not contain any studies with human participants or animals performed by any of the authors.

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