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(REVIEW ARTICLE)

The evaluation of denoising techniques on microscopic blood smear images of Acute Lymphoblastic Leukemia (ALL)

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Abstract

Preprocessing is the first step in the image processing for any digital image before it goes further step. Denoising techniques are one of the important techniques used in preprocessing. The digitized microscopic blood smear image contains unwanted noise due to poor illumination, electronic interference, different variation in lighting condition etc. The processing of these images without the filtering techniques, can produce inaccurate results in the further step of image processing such as segmentation, feature extraction and classification. So, it is necessary to preprocess the images with proper techniques for each type of preprocessing. In this paper, we have tried to evaluate the different types of the filtering techniques on the blood smear images of Acute Lymphoblastic Leukemia (ALL) for the removal of noise. We have reviewed many research work which have used various filtering techniques used for removal of noise.

Keywords: Acute Lymphoblastic Leukemia; White Blood Cells; Myelogenous; Median Filter; Gaussian filter; Wiener filter; Average filter; Bilateral filter

1. Introduction

Acute Lymphoblastic Leukemia (ALL) is a form of malignancy that impacts both the blood and bone marrow. It is caused by an excessive amount of immature white blood cells called *lymphoblasts*, which are unable to function normally and can crowd out normal blood cells in the bone marrow. This type of disease commonly seen in the children as well as in adult people. *Cancer* is the second-greatest cause of mortality in the world, behind cardiovascular diseases, and leukemia is one of the most prevalent amongst blood diseases. Cancer is the second highest cause of death worldwide, according to data from the *World Health Organization (WHO)*, with a total mortality rate of approximately 9.6 million in 2018[1,2]. There are roughly 1.24 million new cases of blood cancer diagnosed each year around the world, which accounts for approximately 6% of the total number of cancer diagnoses [3]. The American Cancer Society predicts the following for the number of cases of *Acute Lymphoblastic Leukemia (ALL*) among children and adults in the United States in 2023: approximately 6,540 new cases of ALL will be found in which 3,660 are men and 2,880 are women and approximately 1,390 ALL fatalities in which 700 death of males and 690 deaths of females. The probability of being diagnosed with ALL is highest in children less than 5 years old. The risk then decreases gradually until the mid-age of 20, and then begins to rise gradually again after age 50. Approximately 40% of ALL cases are diagnosed in adults [4]. There have been reports of age-adjusted incidence rates as high as 102,3 per million for males and 101,4 per million for girls in India. The incidence of ALL increases between the ages of 2 and 5 years and is slightly higher among boys. Children with ALL are much more likely to survive because of understand more about the pathogenesis and genetics at the molecular level, applying risk-stratified treatment, and have access to novel therapeutic drugs. The overall survival rates for children at five years have increased up to 89%. In India the Overall survival rate of children with ALL has been estimated at 45-81% [5]. If left undetected, the disease may progress rapidly and leading to fatalities within months. However, with appropriate testing and medication, ALL can be cured in the majority of cases.

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Technology has been used for the diagnosis of various diseases. Machine learning and Deep learning has been found to better technologies for the same. Several research has been conducted but yet there is a need of improvement.

In our project, we have collected some open database of ALL images for diagnosis using Deep Learning. Specifically in this paper, we have focused on the noise removal techniques while preprocessing the image. The paper has been divided in to sections as follows

I. Introduction II. Acute Lymphoblastic Leukemia (ALL) III. Challenges in Acute Lymphoblastic Leukemia (ALL) IV. Literature Review and V Conclusion

2. Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is a kind of blood cancer that begins in the white blood cells in the bone marrow, known to be the soft tissue within the bones in your body. It begins with immature lymphocytes, that are a form of white blood cell that are essential for the functioning of your immune system.

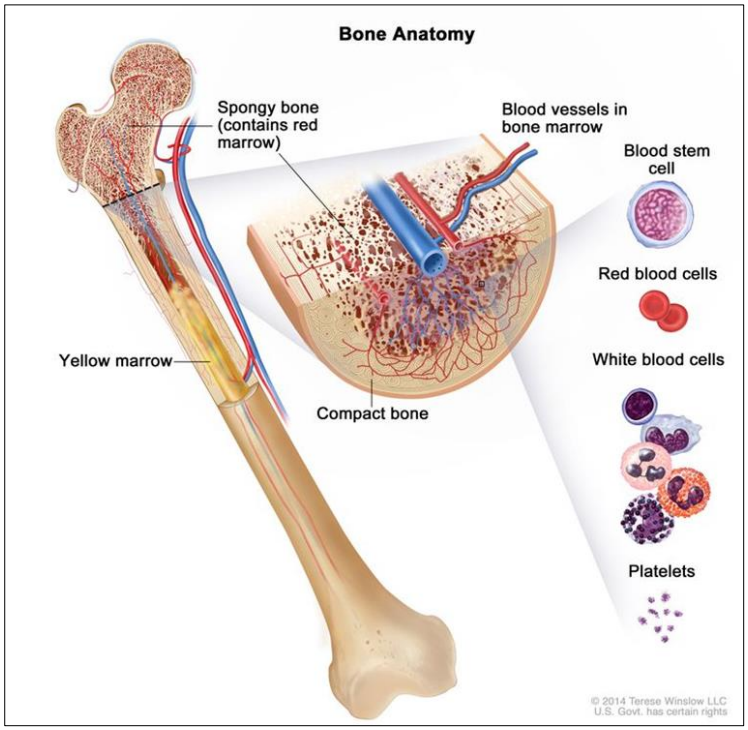

Figure 1 Anatomy of the bone [58]

Fig 1 indicates the anatomy of the bone. There are three main parts to a bone: compact bone, spongy bone, and bone marrow. compact bone forms the outermost layer of the bone. Red marrow is found primarily in spongy bone, which can be found at the ends of bones. Bone marrow is a form of connective tissue in bones that contains blood vessels. Both red and yellow bone marrow are present. Red blood cells, white blood cells, and platelets all originate from blood stem cells, which are located in the bone marrow. Yellow marrow is mostly fat.

Fig 2 indicates the development of blood cell, where blood stem cells, also called hematopoietic stem cells, are found in bone marrow and may differentiate into many various types of blood cells. These stem cells can turn into myeloid and lymphoid stem cells, which are the two primary types of precursor cells. Myeloid stem cells turn into red blood cells, that carry oxygen to the body's tissues as well as white blood cells also known as Granulocytes, , which are essential for fighting infections , and platelets, which help in blood clotting.

Lymphoid stem cells, on the other hand, turn into lymphocytes, a type of white blood cell that is very important to the immune system. B cells and T cells are the two main types of lymphocytes. B cells produce antibodies, which assist in identifying eliminate pathogens that are trying to get into the body. T cells, on the other hand, attack infected or

abnormal cells in the body directly. Natural killer (NK) cells are a crucial part of the immune system's defense against cancer cells and viruses.

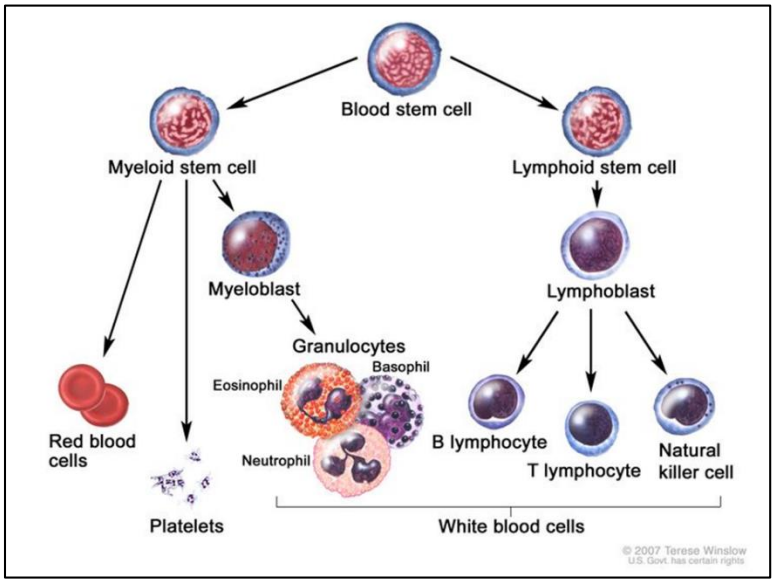

Figure 2 Several stages are involving in the transformation of a blood stem cell into a red blood cell, platelet, or white blood cell in development of blood cells [58]

The development of acute lymphoblastic leukemia (ALL) and its effects on the body is discussed further. ALL is a blood and bone marrow cancer that is distinguished by an excessive number of immature lymphocytes, also known as lymphoblasts. In a healthy individual, the production of blood cells is strictly controlled and balanced, with new cells forming as needed for the replacement of old or damaged cells. In ALL, however, this process is disrupted, and an excessive number of stem cells develop into abnormal lymphoblasts rather than healthy blood cells. The inability of these lymphoblasts to function properly and develop into fully functional white blood cells weakens the immune system's ability to defend against infections. Since the amount of leukemia cells in the blood and bone marrow increases, there is less space for the production of healthy blood cells, such as red blood cells, white blood cells, and platelets. This may give rise to anemia and thrombocytopenia that result in a shortage of red blood cells and platelets, respectively.

A complete blood count (CBC) testing is main technique for diagnosing the acute Lymphoblastic leukemia (ALL). This test is performed on different forms of red blood cells, white blood cells, and platelets in the body. The CBC may reveal abnormal numbers and different form of white blood cell and a small amount of red blood cells and platelets, among people with ALL. If the CBC indicates leukemia, typically additional testing is carried out to confirm the diagnosis. This could involve a bone marrow biopsy, during which a small amount of bone marrow is taken out and examined for leukemia cells under a microscope. Examination of blood and bone marrow samples manually requires a physician with a great deal of expertise in order to make a diagnosis of leukemia. In ALL, blood forming tissues are affected, become a cancerous and begin to produce abnormal *White Blood Cells (WBCs).* Different kinds of leukemia are distinguished by the following criteria: i) Leukemia is based on the type of infected WBCs: It is classified as *lymphoblastic or myelogenous* depend on different kind of WBCs that are infected. In lymphoblastic leukemia, abnormal growth of *lymphocytes*, whereas in myelogenous leukemia, abnormal growth of *granulocytes* and *monocytes* collectively which known as myeloid cells ii) Leukemia is categorized into two types such as acute and chronic, it is based upon whether the majority of abnormal cells are embryonic or mature. In *Acute leukemia*, the majority of aberrant cells are immature, whereas the majority of abnormal cells in *Chronic leukemia* are mature. Acute leukemia grows rapidly since it generally impacts immature cells. Chronic leukemia, on the other hand, is less severe and advances at a slower pace as compared to acute leukemia. The leukemia is categorized into four possible combinations depend upon the lymphoblastic or myelogenous and acute and chronic, so the resulting leukemia are categorized as follows *1) Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), Acute Myelogenous Leukemia (AML), and Chronic Myelogenous Leukemia (CML)*[6]. Figure 3: Indicate the types of Leukemia

Acute lymphoblastic leukemia (ALL) can be divided into two cells such as B-cell acute lymphocytic leukemia (B-ALL) and T-cell acute lymphocytic leukemia (T-ALL) [37]. Acute Myelogenous Leukemia (AML) is a form of malignancy which damages the stem cell precursors in the myeloid lineage. Myeloid cells are cells that develop into red blood cells,

platelets, and different types of white blood cells, excluding B cells or T cells. AML is a highly serious form of leukemia as the abnormal cells develop rapidly and prevent the bone marrow from performing normally [38]. Chronic Myelogenous leukemia (CML) is kind of myeloproliferative neoplasms consist a set of disorders in which blood cells at different stages of maturation becomes out of control in the development of blood cells in the bone marrow [39,40]. Chronic lymphocytic leukemia (CLL) is an aggressive form of cancer that affects mature B cells, especially CD5+ B cells, which accumulate within the blood, lymphoid tissues, and bone marrow [41]. CLL constitutes one of the most prevalent forms of blood cancer in adults, and older people are more inclined to be diagnosed with it. Some people with CLL have absence of the p53 gene, also known as a tumor suppressor gene that controls cell growth and prevent cancerous cells from developing. A deficiency of p53 can cause cancer cells to grow out of control and increase the risk that they won't respond to treatment [41,42].

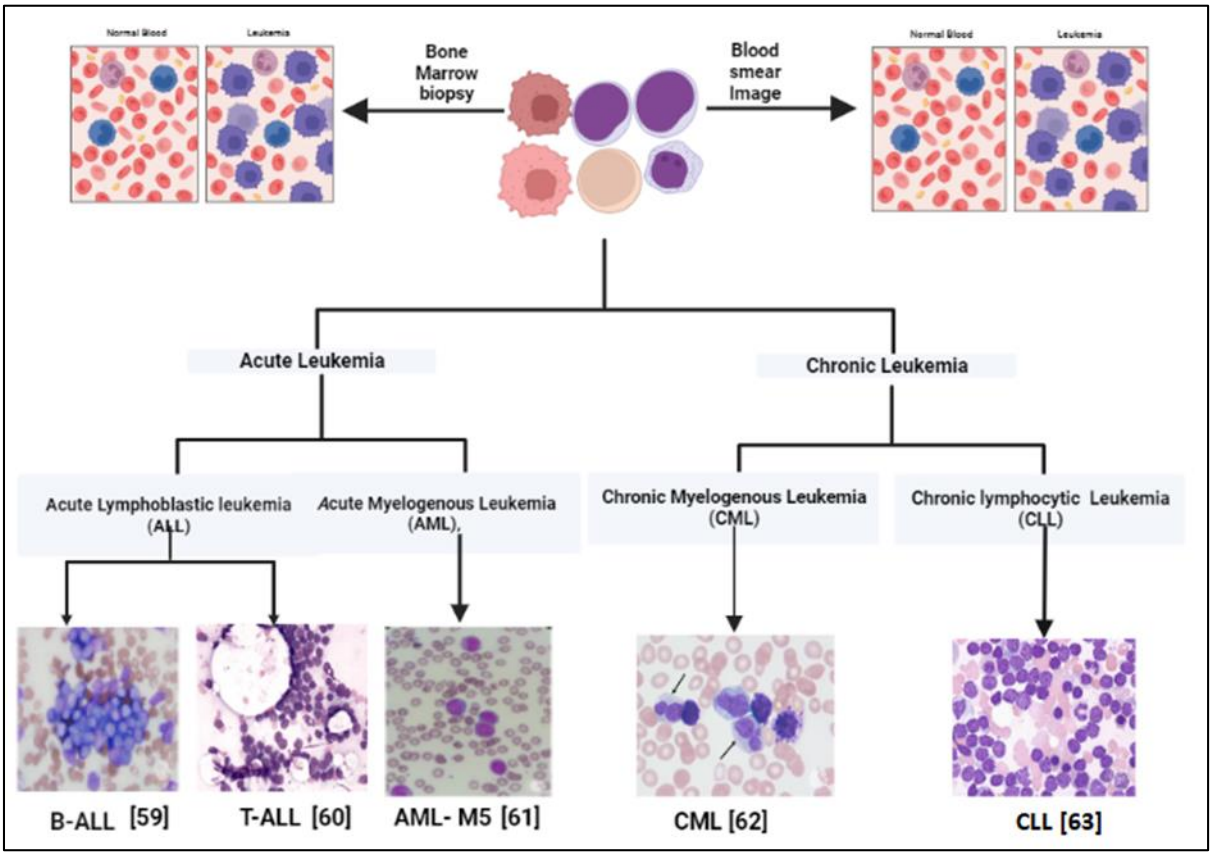

Figure 3 Indicate the Types of Leukemia

3. Challenges in Acute Lymphoblastic Leukemia (ALL)

3.1. Challenges faced by the domain experts

There are several types of challenges that must be addressed in the identification, treatment, and management of acute lymphoblastic leukemia (ALL). Some of the challenges are faced by domain expert are as follows:

3.1.1. Subtypes and genetic heterogeneity

Adolescents and adult have a lower likelihood of developing ALL, their overall survival rates are lower if diagnosed and their long-term prognosis is worse compared to that of children. Therefore, ALL remains challenging to eradicate in adults as well as adolescents. The lower occurrence of genetic subtypes associated with an acceptable outcome and corresponding rise in subtypes associated with a favorable outcome are key factors influencing prognosis in this population. Each of these subtypes possess different prognoses as well as treatment requirements. Accurately determining the subtype of ALL is necessary for developing effective treatment approaches. [43]. The occurrence of ALL in adults is lower than in children. Adults with ALL can be difficult to diagnose because of the disease's lower prevalence and overlapping symptoms with other diseases. Additional comorbidities in adult patients may further complicate therapy strategy [44].

3.1.2. Relapse and resistance

Relapse remain a significant challenge in ALL, despite advances in treatment. Relapse or refractory disease may arise when a patient's cancer no longer responds to chemotherapy or targeted therapies. Research is currently underway to find techniques to overcome treatment resistance and prevent relapse [45].

3.1.3. Treatment-related toxicities

The intensive chemotherapy treatments used for the treatment of ALL may result in significant adverse impacts on the patient's health. Long-term complications may result in secondary cancers or infertility, and short-term effects can include suppression of bone marrow, a higher chance of infection, and toxic effects on organs [46,47].

3.1.4. Involvement of Central nervous system (CNS)

The central nervous system (CNS) is a common target for Acute Lymphoblastic Leukemia (ALL). Specialized treatment techniques, such as intrathecal chemotherapy or CNS-directed radiation therapy, are necessary for both the prevention and treatment of CNS relapse [48].

In order to overcome the above challenges faced by the domain experts, a multidisciplinary approach including different types of diagnosis will need to be implemented, such as blood smear analysis, flow cytometry, genetic analysis, and imaging studies. The precision and reliability of blood smear examination in the diagnosis and management of ALL can be increased through standardization of the criteria for diagnosis, training of medical professionals, as well as ongoing research into the biology of ALL.

3.2. Technological Challenges faced by the technical experts during analysis of Blood smear images of ALL

Blood smear examination is an essential tool for identifying and monitoring of acute lymphoblastic leukemia (ALL). However, technical experts face a number of technological challenges when analyzing these images, which can have an effect on the accuracy and reliability of the diagnosis. Some examples of these challenges are as follows:

3.2.1. Low sensitivity

Blood smear image analysis can have a low sensitivity to detect ALL, especially in cases of minimal residual disease (MRD). MRD indicates that there are cells that are malignant in the blood or bone marrow at very low level, below the threshold of detection by traditional microscopy. MRD may need to be found in ALL using more sensitive methods, like flow cytometry or polymerase chain reaction (PCR) [49].

3.2.2. Inter-observer variability

Blood smear images can be difficult to comprehend because they may be interpreted differently by different people. This can make it difficult to determine how to properly treat and diagnose an individual. Inter-observer variability can be reduced by standardizing blood smear analysis and training healthcare professionals [50].

3.2.3. Morphologic variability

There can be substantial overlap between the morphologic features of ALL images and those of other hematologic disorders. Due to this, a diagnosis of ALL on the basis of a blood smear image alone may be difficult. It's possible that further testing, like flow cytometry or genetic analysis, needs to be performed to confirm the diagnosis [51].

3.2.4. Limited information of prognostic

In ALL, prognostic information from blood smear examination may be limited. Some morphologic features, like a high blast count or a particular cytoplasmic or nuclear feature, have been related to a poor prognosis, but other factors, like genetic abnormalities or the patient's response to treatment, may be more informative [52].

3.2.5. Inadequate sample quality

The quality collection of samples and preparation are essential for accurate outcomes when analyzing blood smears images. Blood smear images may differ in quality and difficult to interpret depending on a number of factors. These include cellular clumping, poor staining quality, and low cellularity [53].

3.2.6. Manual interpretation

Blood smear images of ALL are manually examined and analyzed by a trained pathologist or hematologist. This process can be time-consuming and subject to inter-observer variability [54].

To overcome the above challenges faced by the technical expert by using the deep learning and machine learning techniques to automate the examination of blood and bone marrow samples that will enhance the precision as well as the speed of determining ALL. Deep learning algorithms can accurately identify and classify leukemia cells in large datasets of annotated blood smear images [55]. These algorithms can also detect ALL-related morphologic features that humans might fail to recognize. Machine-learning systems can identify ALL-related gene mutations and chromosomal abnormalities in genetic data [56]. Deep learning and machine-learning systems can automate blood and bone marrow sample analysis, accelerating diagnosis and treatment. To ensure clinical accuracy and reliability, these systems need large and diverse datasets for training and validation and rigorous testing [57]. Also, these systems are not meant to replace the expertise of medical professionals, but rather to work in conjunction with them to make better diagnoses and treatment recommendations.

Computer aided system is used detect the acute lymphoblastic leukemia form the microscopic blood smear images, the system takes an input and perform morphological analysis on the leukocytes present in the image and classify them into normal cell or leukemia cell. As state earlier, the primary step before classification is processing and, in this paper, we have narrowed down to one of the preprocessing techniques as denoising technique.

4. Literature Review

During image acquisition from a digital microscope camera, the images can be affected by random noise. This noise can be caused by various factors, such as electronic interference, thermal noise, or variations in lighting conditions [7]. Many researchers use noise removal techniques from the images by applying the various types of filters. Ahmed I A. et al. [8] used average filter size of for removing a noise and artifacts. The average filter factor is set 6 X 6 and performed rotation on each image, calculating the average value of neighbor pixels for optimizing one target pixel, this filtering process is repeated over each image pixel. The enhance images is fed in to Laplacian filter to display the edges of WBC cell and improve the low contrast among the WBC cells and cytoplasm. Devi T G and Patil N [9] implemented the two filters Weiner and Median filter for the comparison of accuracy in denoising the images using the PSNR value for the better classification of cells. They have found the Median filter is 8% better than the Weiner filter. Jyoti R et al. [10] used the histogram equalization for enhancement the image quality and order statistic filter for the removal of the noise and smoothing of the image. Karthikeyan T and Poornima N [11] proposed adaptive median filter for elimination of the noise from the blood smear image. Nameirakpam D et al. [12] used median filter for the removal of the unwanted noise in the segmentation phase because after the segmentation done over the image some of the noise is still present. Abunadi I, Senan E M [13] used two filter namely – average filtering for the removal of the noise from the image and Laplacian filter to enhance the edges contrast, The average filter of size 6 X6 is applied over the image until image get smoothen. Waghela J A [14] use Gaussian blur technique for the reduction of the noise from the image and this technique using the Gaussian function for the smoothing the image. Mohapatra S et al. [15] used selective median filtering for removal of noise from image. Mishra S et al. [16] used the Weiner filter for noise removal from microscopic blood smear image from ALL-IDB database. Patel N and Mishra A [17] used median filter for eliminating the noise from the image and wiener filtering for eliminating the blurriness in the image and measure the amount of cleaning done in the image by mean solidity where the area and convex area of the leucocyte has to measured. T. Patil T G and Raskar V [18] demonstrates how the selective median filtering for eliminates image noise followed by unsharp masking techniques which effectively used for enhancement of sharpness of the images. Joshi M M D et al. [19] used 3X 3 minimum filter to decrease noise and maintaining image edges and enhancing contrast around nuclei of the image. Al-Hayali L M et al. [20] used Median filter, a popularly known for the order-statistics filter used to eliminate noise while maintaining sharp edges with lesser blurring than linear smoothing filter of same size. Chitra P et al. [21] used Adaptive Weighted Mean Filter (AWMF) for the reduction of the noise from the image, after filtering applied the edges get blurred so the edges can be enhanced by applying histogram technique to improve the contrast of the image. Hazlyna H N et al. [22] used fusion method consist of 7x7 median filters and seeded region growing area extraction (SRGAE) method for eliminating the unwanted noise from the image, The benefits of this combination technique are that it is more efficient and performs effectively to remove salt and pepper. Yan Li et al. [23] combined the mathematical morphology and median filtering for reduction of unwanted noise and eliminate inadequate WBCs components. Toh L B et al. [24] proposed a median filtering method for the removal of the noise that appears in the segmented image after processing the thresholding. It has been studied that the median filter with a size of 7X7 proved to be more adequate for the elimination of pepper noise, preservation of the edges of the blast cells, and filling up the small holes in the segmented image. Bennet Rajesh M and Sathiamoorthy S [25] applied a median filter to eliminate the salt-and-pepper noise without blurring the edges

of the image. Shirazi S H et al. [26] used Wiener filter to get rid of the noise and blur in the image. The main advantage of this filter is that it preserves the edges of the image, which is important for precisely segment the object from the noise. The Wiener filter can't be applied directly on a 3D image, so they divided the YUV channels and then employed the Wiener filter on the V channel. Gebremeskel K D et al. [27] used Gaussian filter to alleviate the effects of camera noise as well as erroneous pixel values and Wiener filter to eliminated of these noises and de-blur the image. Kandhari R et al. [28] convert the RGB image into HIS (Hue, saturation and intensity) image. The H- Plane contain the rich set of information as compared to other planes. The H-plane is then preprocessed by using Gaussian filter, selective median filter, order statistical filter, Gaussian bilateral filter for the removal of the noise s i.e., background noise, salt-and-pepper noise etc. from the image. They have found that Gaussian bilateral filter is the best filter among all filters Hamza M A et al. [29] proposed the optimal deep transfer learning-based human-centric biomedical diagnosis model for acute lymphoblastic detection (ODLHBD-ALLD), that employs the Gabor filtering (GF) method to get rid of noise in the detection and classification of acute lymphoblastic leukemia in a blood smear image. Kaur R and Maini R [30] used different types of filters such as Median filter, Adaptive filter, Alpha Trimmed Mean Filter (ATMF), Contra harmonic Mean Filter (CHMF), and Bilateral filter over the noisy image such Salt and Pepper noise, Gaussian noise, Poisson noise and Speckle noise. The PSNR value has been calculated for each filter with respect to the different noises present in Leukemia Images. They have found that the Median filter show the better result among all filters. G. Mercy Bai G and P, Perumal V [31] used Gaussian filter which is most effective technique for removal of the noise and smoother transition of the image. Veeraiah N et al. [32] use histogram equalization, Gaussian filter and bilateral filter for lowering the noise, preserving the edges in the image and eliminated specific distortion and additional details from the image. Abuhayi B M and Mossa A A [33] preferred the Gaussian filter because it is found the most suitable filtering algorithm for the removal of the noise like variations in brightness, illumination, and distortion rather than Median filtering and Adaptive Median filter. Azza M B A et al. [34] used Linear scaling filter for the removal of the noise from the image. Pałczyński K et al. [35] used Gaussian blurring method along with median for reduction of the noise in the image and creation of low pass filter. Singh G et al. [36] applied the Gaussian filter for the removal of the noise and increase the Signal-to Noise Ratio (SNR) to improve the accuracy for identification of ALL effectively.

From the above literature survey, we have illustrated in the figure 4 (a) the different types of filters (in term of Percentage wise) for the removal of noise from the image and Figure 4 (b) the Histogram representation in terms of Numbers of Papers with respect to different types of Filtering Techniques

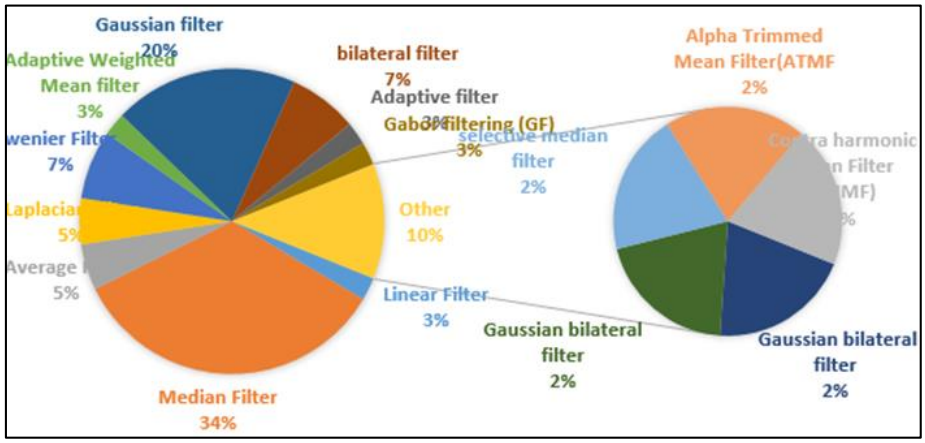

Figure 4 (a) Pie-Chart representation of different types of Filtering Techniques

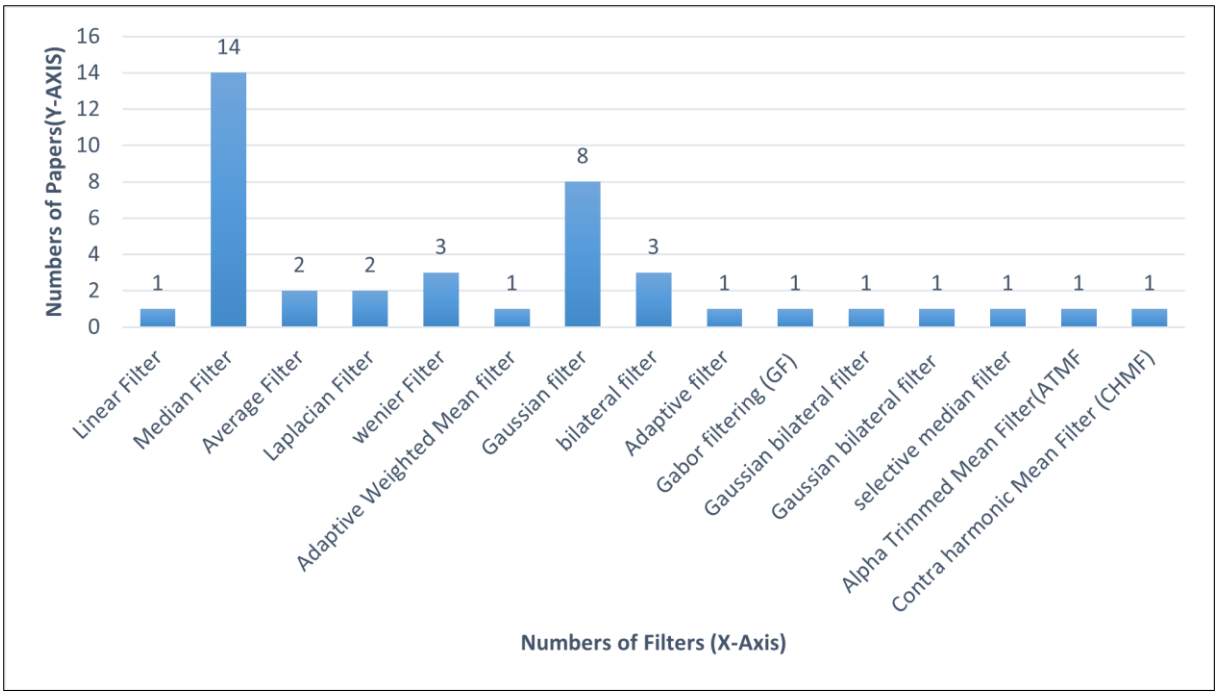

Figure 4(b) Histogram representation of different types of Filtering Techniques

In paper, 36 research papers have been reviewed and analyzed based on denoising techniques and the evaluation is shown in Fig 4(a) where it shows 34 % Median filter, 20 % Gaussian filter, 7% Weiner filter, 7 % bilateral filter, 5% Laplacian filter, 5 % Mean filter are used as denoising techniques.

Fig 4(b) show, from 36 Papers, 14 papers used Median filtering technique, 8 papers used Gaussian filtering technique, 3 papers used Weiner filtering and Bilateral techniques, 2 papers used Laplacian filtering and Average filtering.

5. Conclusion

From the literature survey, we have found that Median filter is used by many researchers for the removal of the noise from the blood smear images followed the Gaussian filter. So, it has been observed that the Median filter is used heavily among all filters for removal of the noise. Even though the Median filter is used for elimination of the noise, it has some limitations that could affect the performance when it's applied to blood smear images. One of the important limitations is to blur or remove important details and features from the image such as edges, cells, and other structures. The effectiveness of the median filter depends upon the size of filter kernel. So, if the larger kernel is applied over the image more noise is removed from the images and more important details will be lost from the image. On the other hand, if the small kernel is applied to the images, it could not be effective enough to get rid of the noise in the images. So, it's important to select an appropriate kernel size to determine an appropriate balance between reducing the amount of noise and preserving essential information and features. The authors will be proceeding with the right kernel size selection for denoising and also enhance the image with contrast enhancement, brightness, sharpening and smoothing. This research on successful completion along classification will lead for a support system to be used by medical practitioners in reducing the mortality rate of ALL patients.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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