A review of Microfluidic blood separation techniques

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Abstract. Microfluidic blood separation is a modern biological technology used to separate blood cells from their fluids. Blood cells present in the blood become an important outline of many diseases. To maintain the stability and sterility of blood, a tool with renewable technology and a large capacity is needed. Microfluidic blood separation has important assets, especially changes in the physicochemical properties of blood cells that are used for quick and accurate clinical diagnosis. Dissemination of structural materials and compositions from the separation and sorting of blood uses a technical system that will create this optimal microfluidic blood separation in research. As for this paper structure starts with introduction, then continued with literature review, type of Microfluidic methods, application of Microfluidic, and bibliometric analysis. With those methods the result could be conducted with systematic literature reviews. Therefore, this study is prepared to identify research gaps in topics related to Microfluidic blood separation techniques. Related studies about microfluidic blood separation techniques are identified using bibliometric analysis and systematic literature review of the study search index through database Scopus-indexed publications. The results from this paper reveal the topics in urine as a parameter for Microfluidic separations as the research gap according to Microfluidic separations. This paper expects research on Microfluidic blood separation techniques will continue to be developed to maximize the potential of Microfluidic blood separations in helping the research process.

1. Introduction

The development of technological devices that have the function of liquid or substance separators has grown massively over the years. In the modern medical industry, liquid or substance separators are used for various purposes. One of those purposes is to separate the composition of blood plasma through microbiological fluids separators known as microfluidics devices. These microfluidics devices enable people to operate one of the most common blood tests: complete blood count (CBC) [1]. CBC tests provide crucial information to determine the overview of a patient's health conditions seen through the concentration of any substances contained in the blood, such as protein, creatine, or metabolites [1]. Generally, the conventional way to run the CBC test was inefficient considering it was time-consuming for the patient to receive the result. Therefore, microfluidics devices are introduced to overcome those issues through a more simplified process either with an active separation method that uses external forces including microelectromechanical systems or a passive separation method that does not use any mechanical forces [2].

Numerous microfluidics devices of both active and passive methods that are used for liquid or any substance separator have been produced in many forms of improvement. The variety of materials used to build microfluidic devices is one of the improvements that have been established over the years. According to some research, microfluidics devices were initially produced in silicon and glass material [2]. However, these materials have an issue with their opacity in the Ultra-Violet or Visible (UV/Vis) region of the spectrum in the electromagnetic mechanism. The cost of the manufacturing processes for microfluidics using silicon or glass material is also relatively high. Therefore, the need of a new alternative material and manufacturing process for microfluidics are in a high demand.

This study is prepared to provide an alternative way to produce microfluidic devices with lower production costs so that it can be more affordable for medical usage using polymers and elastomers. Polymers and elastomers are less expensive than silicon and glass material. Adding to that, polymers and elastomers are also easy to mould and emboss. Hence, the material can be moulded using a 3D printing machine to reduce the cost of the operation for microfluidics. This way, microfluidics function can be accelerated at an overly reduced cost.

2. Literature review

2.1 Type of Microfluidics method

Microfluidics is a technology which develops certain fields such as chemistry, biology, and medical equipment

that are still in development [3]. Microfluidics are often used to separate different components of blood using microfluidic devices. Microfluidics has several methods for developing this research, some of which methods are listed in Table 1.

Table 1. Type of Microfluidic methods.

Type of Microfluidic Methods		
No	Method	Brief Description
1	Traditional method	Blood separation method with a long processing time but have a disadvantage such as high cost, and others.
2	Flow focused microfluidics	Uses manipulation of the flow of liquid in a microscopic channel with the aim of targeting the sample at a point.
3	Micro particle image velocimetry	Measurement of three-dimensional microfluidic flow velocity based on stereoscopic imagery.
4	Droplet microfluid	Manipulating liquids in the form of microscopic droplets.
5	Organ-on-chip microfluidics	Manipulating cell cultures in microscopic channels with the goal of constructing organ models at the microscale.

The traditional method of blood separation has a long processing time, expensive capital costs, low throughput, high sample volume, and requires skilled technicians because it involves centrifugation. The blood microfluidic separation process involves the use of special channel designs and basic chemistry knowledge to selectively separate different blood components such as white blood cells, red blood cells, and plasma. For example, in microfluidic devices for plasma separation, the surface of the device can be designed with specific chemical arrangements that specifically bind to plasma proteins to allow plasma to be selectively captured at this stage and other blood components past this stage.

Blood plasma self-separation is divided into two categories based on the driving mechanism of separation, namely:

- Separation by density. This separation is accomplished using difference in density between plasma and other blood components blood cells. Plasma, which is less dense than the other components, can be separated from the plasma by letting the blood settle, then the plasma will rise to the top. This process is known as sedimentation and can be enhanced by centrifugation or by using special microfluidic designs that support settling.
- Separation by surface (traditional method). This separation is carried out using the selective binding of plasma proteins to a specific surface or chemical regime. For example, the surface of the device is regulated using a specific chemical arrangement that specifically binds to plasma proteins, allowing plasma to be selectively captured while other blood components pass through the device. This process is also known as affinity-based separation, which is driven by selective interactions between specific molecules in blood and chemical arrangements on the surface of the device.

Blood plasma sequestration can be further divided into two subcategories, namely: active segregation and passive segregation [4].

- Passive segregation is the segregation of plasma from the rest of the blood that occurs without any external force or energy input. These methods of passive separation usually rely on intrinsic physical properties of blood, such as its density, surface tension, or viscosity to drive the separation process. Examples of passive separation methods are density gradient centrifugation and sedimentation-based separation.
- Active segregation is the energy input used to drive the separation process. Examples of active self-separation methods include affinity microfluidic separation, microfluidic dielectrophoresis, and microfluidic acoustic separation.

There are differences between the active and passive methods. The active method employs external influences such as electric, magnetic, acoustic, and optical forces to break apart cells. On the other hand, the passive method uses hydrodynamic forces and channel channels to manipulate cells. Both active and passive methods are required to break apart biological cell samples with a high degree of difficulty and complexity. Hybrid microfluidics has become a solution that utilizes both active and passive methods simultaneously to meet higher requirements for stability, convenience, and performance. Other factors involved in the use of hybrid microfluids include the (I) ability to process multi-target cells, (II) higher sensitivity, (III) increased capability for multiplex separation, (IV) and tunability for a wider operational range [5].

Passive and active separation methods have their advantages and limitations. Passive separation methods have the advantages of being simple, low cost, and need minimal equipment. However, these methods may not be as precise or efficient as active separation methods and may require a longer separation time or a larger sample volume. In contrast, active dissolution methods are highly precise, efficient, and adaptable to specific plasma components. However, they require special equipment that may be more complicated and expensive to conduct research [4].

Several blood microfluidic separation methods have been reported in the literature of some research, including passive methods for size-based separation, inertial separation, and deformability-based separation, and active methods such as dielectrophoresis and electrokinetic separation. Numerous techniques for microfluidic separation have been utilized for the purpose of isolating bacteria from blood cells, including dielectrophoresis (active segregation), inertial effects, surface acoustic waves, cell margination, bead-based extraction, filtering, centrifugal microfluidics, and lysis-

based methods [6]. Separation by size is the most widely used method for blood separation, which separates blood components based on their size differences [7]. Inertial separation and deformability-based separation use the inertial and mechanical properties of blood cells to separate blood components, respectively.

Dielectrophoresis (DEP) is another active microfluidic method for blood separation, which makes use of the differences in the electrical properties of blood components. Electrokinetic separation, on the other hand, employs differences in the electrophoretic mobility of blood components. Several microfluidic devices have been developed for DEP and electrokinetic separation and have shown promising results for blood separation [8].

Microfluidic devices have demonstrated high separation efficiency, small sample volumes, and easy integration with other analytical tools. Microfluidic blood separation is also a rapidly developing field that has the potential to revolutionize medical diagnostics and therapy. Microfluidic devices provide a platform for efficient and rapid separation of blood components, which can be used for a variety of applications like disease diagnosis, drug discovery, and blood transfusion. Through bibliometric analysis and systematic literature review, it is evident that research on microfluidic blood separation has increased significantly in recent years. There will be developed interest in the development of new microfluidic devices, optimization of blood separation methods, and integration with other analytical techniques. In addition, the literature indicates that much remains to be explored in this area, including the scalability of microfluidic devices, reproducibility of results, and translation of this technology into clinical settings [9].

Soft embossing and PDMS offer advantages compared to other materials and techniques in terms of affordability, simplicity of fabrication, and efficient processing time. This makes soft embossing and PDMS a suitable prototype for conducting research on microfluidics. Furthermore, the low tensile modulus of PDMS offers advantages for microfluidic applications such as demolding features in micro-scale without damage and the ability to design pressure-actuated valves. The PDMS chip exhibits an average capture rate of 72.8% for a sample size of 500 particles. Particle capture takes place at the outlet of the chip in the last three reservoirs. Particles are first captured by the reservoir near the inlet then more beads are injected, more are caught along the channel. A 99% capture rate for beads occurs in the first nine reservoirs. It can be concluded that only nine reservoirs per channel are required, instead of 12 reservoirs per channel.

2.2 Application of Microfluidic

Based on some research, it is proven that microfluidic technology has been an effective solution to detect medical problems. Microfluidic can be used for CBC tests, cancer diagnosis, circulating tumour cells (CTCs), metastatic colorectal cancer (CRC), and other various blood plasma-related medical tests. Each test has different methods from one another even though the test was held with microfluidic. Several different methods for each medical test as the application of microfluidic function in the medical field are shown in Table 2.

Table 2 Type of Microfluidic methods in medical test.

Type of Microfluidic Methods in Medical Test		
No	Test	Method
1	Cancer diagnosis	Biosensor and microfluidic incorporation.
2	Circulating tumour cells (CTCs)	Manipulating various geometries and architecture of microfluidics chips.
3	Complete blood count (CBC)	The passive method with micro-trench along the low path.

Microfluidics as a CTCs test has been validated as a companion diagnostic tool that is used for monitoring the therapeutic response in patients and for conducting the prognostic evaluation [10]. Therefore, microfluidics application can be seen through CTCs tests for cancer diagnosis, especially colorectal, breast, and prostate cancer. The implementation of microfluidics in CTCs enrichment can go through the positive or negative-immune selection. However, the study shows that plenty of positive selection microfluidics chips that have been constructed in various geometries and architecture can exhibit over 90% of capture efficiency after a few tedious sample pre-processing steps. Hence, the incorporation of biosensors and microfluidic resulted in the feasibility to detect the panel of protein biomarkers as an expanding sensor in cancer diagnosis cases [11].

Another application of microfluidics implementation in the medical field is CBC. Microfluidics has the role of separating the blood plasma through sedimentation so that it enables plasma purification for further analysis [1]. Those purifications are categorized into three main compositions: whole blood inlet that contains a plasma zone, buffer inlet that contains red blood cell (RBC) zone, and bifurcation region that contains white blood cell (WBC) zone. Once the categorization was done, the classification can go further to know the type of antibody so it can be used to determine the blood type of the patient [1].

2.3 Bibliometric analysis

Bibliometrics analysis is The interdisciplinary field that employs mathematical and statistical techniques to quantitatively analyze information across different domains of knowledge [12]. Currently, bibliometric analysis has become a popular method used by many researchers. This can be observed in one of the databases, namely Scopus, where the search results using the keywords "bibliometric analysis" on 11/04/2023 show that there have been 7,744 publications implementing bibliometric analysis from 2022 to 2023. There are several reasons why researchers nowadays utilize bibliometric analysis as one of their research methods. One of the reasons is to observe the trends and patterns in various emerging research, and to explore scientific literature comprehensively. Additionally, bibliometric

analysis can be employed to understand the interrelationships between topics, generate new unexplored ideas, and etc [13].

Bibliometric analysis is utilized when researchers analyze a large volume of scientific literature publications to analyze. Bibliometrics can aid in analyzing such large datasets by providing summaries using various keywords, thereby assisting researchers in understanding the relationships among different scientific literature [14]. There are many ways to perform bibliometric analysis to help conduct research. Vosviewer in one of the applications to help researcher to perform bibliometric analysis. VOSviewer, a bibliometric analysis tool, has the capability to implement text mining algorithms to identify various data elements within scientific literature, such as abstracts and titles. This allows for mapping through the formation of networks, clusters, and heatmaps, enabling researchers to visualize and analyze the relationships among different publications [15].

3. Methods

Study on biometric analysis and mapping was conducted using the Scopus database on 18 March 2023 to obtain various Systematic Literature Reviews and biometric analyses of previous studies. The data obtained from the Scopus database was related to microfluidic separation. There are various reasons for using Scopus as a database, including its advantages such as having articles, journals, and conference papers with high indexes. The process of finding scientific literature relevant to the research topic, biometric analysis, and systematic literature review will be carried out by narrowing down the search using several keywords. The keywords used in the search for scientific literature in the Scopus database include "Microfluidic," "Blood," and "Separation." The keywords searched for are in the title, abstract, and keywords, so in the Boolean search logic, it is written as TITLE-ABS-KEY (microfluidic AND blood AND separation). All data obtained from Scopus amounted to 1922 documents. Next, the first screening is carried out on the documents located in Scopus. The screening is done by considering various factors such as documents released above 2018, open access documents, documents in the form of journals, articles, and reviews, and documents in written in English. The final screening process with the assistance of the latest software was conducted using Publish or Perish. This was done to find scientific literature that has a relationship with microfluidic separation and has a significant impact. At this stage, the data found will be used for biometric analysis and Systematic Literature Review. The systematic screening process can be seen in Figure 1.

The process of screening literature review resulted in the establishment of several rules for searching scientific literature. The inclusions and exclusions of papers submitted can be seen in Table 3. Throughout the screening process, a final result was obtained, revealing that 33 papers will be used, with 13 of them recognized as key papers. Meanwhile, the other 33 papers will be used for bibliometric analysis using VosViewer application to visualize networks and categorize the obtained keywords. The 13 key papers will be used to create a systematic literature review to provide further knowledge on microfluidic separation.

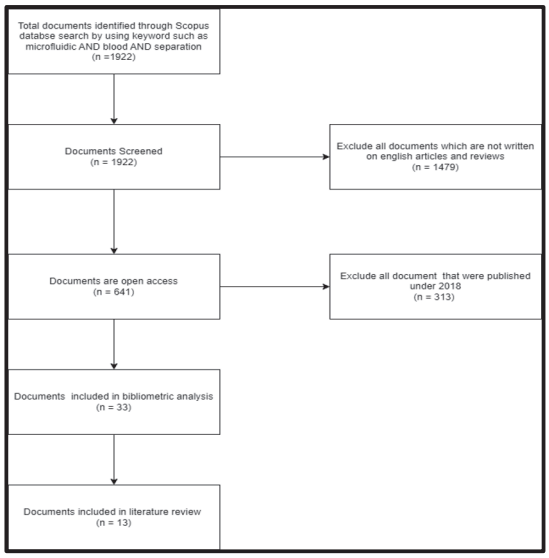

Figure 1. Process of conducting literature review with PRISMA method.

Table 3 Scientific literature inclusion/exclusion criteria.

Inclusion Paper	Exclusion Paper
The scope of the analysis from scientific literature must be focused on microfluidic separation	Outside the scope of research on microfluidic separation
Scientific literature must be journal article or review	Review journal article or review were excluded
Selected scientific literature must be published from 2018 to 2023	Articles that were published under 2018 were excluded
Selected scientific literature must be written in English	Other languanges were excluded

4. Result and discussion

4.1 Systematic Literature Review

Systematic literature was conducted from 13 selected papers using the Scopus database for the topic of microfluidic blood separation to detect disease. Figure 1 shows the process of screening 13 selected papers to delve into the literature review. The selected paper can provide insights into the research outcomes on the topic of microfluidic blood separation. This can aid in resolving future challenges. As evident from various previous studies, microfluidic blood separation has shown potential in detecting various diseases, particularly cancer cells, tumors, and other diseases. Table 4 shows the summary of key papers.

Table 4. Scope of discussion and methods related to battery optimization from selected journal articles based on the search index of the Scopus database.

Type(s) of Approach	Paramaters	Results	Reference
The simultaneous extraction of plasma, red blood cells, and the confinement of white blood cells on a microfluidic chip.	Size, shape, and stiffness of the cell properties since it use passive separation methos	The bifurcation could contain two types of side channels that means it could extract both plasma and RBCs separately with extremely low-volume processes.	[1]
Acoustic impedance to separate bacteria from blood cells with high cell concentrations.	Bulk acoustophoresis with acoustice enrichment and PCR detection to separate bacteria up to 99,7% while removing 99% of blood cells	The process using moderate dilutino and relatively high flow rate can result to the duration of matched acoustrophroresis within 12,5 minutes only.	[6]
Acoustic Microfluidic Separation Techniques and Bioapplications	The separation for the acoustic microfluidic separation using the travelling surface acoustic waves (TSAW) separation has a significant correlation with particle size, density, and compressibility.	Accoustic microfluidic separation techniques could able to seperate microparticles with different physical properties. Also, this techniques could seperate many biological samples such as protein blood cells, cancer cells, bacteria, and viruses.	[16]
Passive microfluidic devices for the separation and sorting of blood cells using various techniques.	For the blood cells seperation process, there are some paramaters that needed to be considered and one of the is the material of which the device made off, such as glass, sillicon, poly (methyl methacrylate) (PMMA), etc.	Material with the highest overall performance for separation is thermoplastics. The recommended technique for separating red blood cells (RBC) is Hemodynamic Separation, which has a separation efficiency of 100% and a plasma separation volume of 15-25%.	[17]
Self-separation of blood plasma during the self-driven flow	There are several factors that can be the paramaters and one of it is the level of the HCT	The experimental results showed that blood plasma separation was effective when using various Hematocrit (HCT) levels within the range of 20% to 34%. However, when HCT levels were increased to 42%, the efficiency of separation decreased.	[7]
The utilization of gold nanoparticles as a sample for the detection of cancer antigens through an interdigitated electrode-based microfluidic biosensor.	Factors that contribute to the detection of cancer on microfluidic biosensors include probe immobilization, specific binding, and the fundamental limits of probe affinity.	Combining microfluidics with biosensing offers several advantages, including the ability to target and separate biomolecules, leading to improved detection during flow and increased signal-to-noise ratio.	[11]
Isolation of circulating tumor cells from unprocessed blood of colorectal cancer patients	There are various factors that play a role in enhancing the success of isolating CTCs from blood cells using microfluidics, such as density, size, deformability, and electrical properties	Microfluidic chips could be able to use unprocessed blood samples to isolate CTCs. The isolation has a high efficiency. The results of the experiment demonstrate that the utilization of fresh samples leads to higher isolation yields and an improvement in sample quality.	[10]
Shear-induced difusion based on novel seperation technique (Passive Separation)	Polysterine Particles in concentrated suspensions	The study describes a new method for continuous focusing and separation of bioparticles directly from human whole blood, which achieved a separation efficiency of approximately 90% with a throughput up to 107 cells per second. The system uses a routine saline solution as buffer and eliminates the need for sample preparation steps, making it a promising technique for diagnostic and prognostic applications.	[18]
Microfluidic method which provides effectiveness and efficiency in testing blood separation research	Parameters involved in the use of soft-lithography technique include temperature, biocompatibility and non-toxicity to cells, surface chemistry, and gas permeability.	Fabrication of microfluidic devices using the soft-lithography technique allowed to growth of microfluidics dield due to the many advantages of this material: high fidelity to replicate by molding features at the micro-scale level, its optically transparent down to 280 nm, low temperature and time to cure, biocompability and nontoxicity to cells, possibility to change surface chemistry according to the application needs, gas permeability allowing culture of cells, and reversal and self-bonding among others.	[2]
Automation of sorting by image based in droplet microfluidics	The parameters for this technique include droplet volume and morphology, as well as size, number, morphology, and intensity of cells.\\	The advantages of using droplet microfluidics for cell encapsulation include reduced reagent volumes, ease of automation with increased throughput and high accuracy, disposable chips, and affordability.	[19]
Isolation of exosomes from blood for diagnose and monitoring pancreatic cancer	Isolation was performed on blood to analyze exosomal RNA. The analysis is based on surface acoustic wave exosome lysis and ion-exchange nanomembrane sensor.	The experiment was conducted using a microfluidic platform, and the results showed a high sensitivity in PC marker detection during exosome capture. This suggests that the sensitivity level of serum samples is lower compared to PC marker detection	[20]

The isolation of tumor cells from urine with localized prostate cancer can be achieved using inertial microfluidics.	Cancer cells, volume of clinical samples urine, anti-Glypican, prostate-specific antigen, and total number of isolated cells	The findings from this study show potential for the spiral inertial microfluidic technique in the diagnosis and prognosis of localized prostate cancer through liquid biopsy of urine. This opens up possibilities for cost-effective, non-invasive and rapid diagnosis, as well as monitoring of therapeutic outcomes in prostate cancer and other urology cancers.	[21]
Using microfluidic technology for cancer applications and liquid biopsy.	Circulating Tumor Cells, ctDNA, and Exosomes	Numerous studies have utilized ctDNA analysis from plasma samples for liquid biopsy applications, with several microfluidic platforms exhibiting promising results. Notably, the CellSearch system remains the only FDA-approved CTC platform.	[22]

4.2 Bibliometric analysis

Bibliometric analysis is a statistical analysis of books, journals, publications, and others. In this study, our team used applications such as VOSviewer and Publish or Perish to find out which journals and publications they wanted further research to support this research. There were 33 publications obtained from filtering existing publications using VOSviewer. Of the 33 publications that have been screened, then we look for sentences that you want to include in this research. After getting the keywords regarding the sentences that you want to aim for or achieve through this research, then we look for more about what topics we will discuss in more depth. There are many topics related to microfluidic devices, including cancer, urine, exosomes, antibodies, separation, isolation, etc. Figure 2 shows the visualization of density data related to microfluidic blood separation.

VOSviewer has analysis and mapping as well as density and overlay visualization to show which topics are most closely related to the topic of microfluidic devices. Density in VOSviewer shows how dense or how many data points are in an area in its visualization. The density or number of data points in a visual area is shown in different colors, depending on the density of each topic. Dense topics have a darker color, and less dense (sparse) topics have a lighter color. Topic density in yellow indicates that topics in visualization have high data density but are rarely discussed for research. All the color topics that will be discussed in this study are listed in Figure 2 Density Visualization of Microfluidic Devices. VOSviewer also has an overlay visualization to visualize data in a greenish yellow color. The brighter the topic that has a yellow color, it means the topic is new in this study.

Through the previous section, we can conclude that one of the newest topics in this study relates to microfluidic research. The conclusion was made by the fact that microfluidic topic is near the bright yellow area. The parameter of the VOSviewer was made based on the 33 other publications that the researchers found during the preparation of this paper relating with the topic that needed to be addressed in this paper, which about the making of microfluidic devices with affordable material. The need of affordable microfluidics devices is in high stake since through the screening of 33 publications, researcher can conclude that the function of microfluidic devices can be useful in many area.

Figure 3 contains several colors including green, yellow, and greenish yellow. The yellow color indicates a topic that is often researched while the green color is a topic that is rarely researched. The opaquer the green color is, the research is rarely or has never been researched. If our group chooses the microfluidic topic, it will relate to cancer, urine, sativa, disease, exosome, etc. Our group chose urine as a topic to be studied in more depth so that our group's focus was only on examining urine in microfluidic device research.

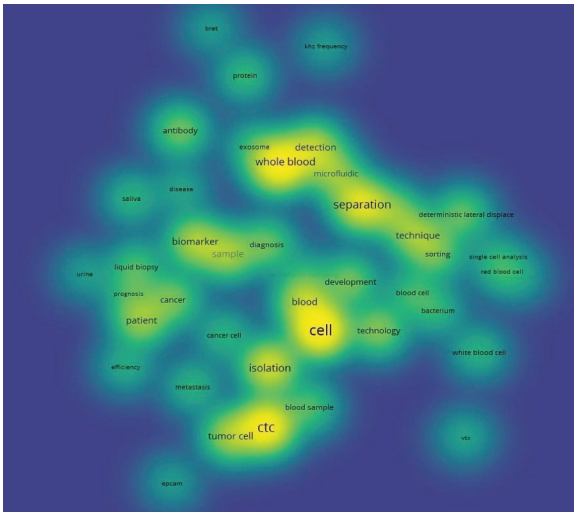

Figure 2. Density visualization of Microfluidic blood separation.

Urine as a research object in microfluidic blood separation can be separated into supernatant fluid and the precipitate using simulated urine samples. Urine contains several types of cells such as white blood cells (WBC), red blood cells (RBC), epithelial cells, kidney-derived cells, and urothelial cells and also protein, vitamin, peptides, genetic material, and inorganic compounds [1]. There are four methods can be use to revealed new opportunities in the fields of research that can improved the feasibility of disease monitoring cause the low fabrication cost. Four methods such as inertial microfluidics, three dimensional (3D) traps for capturing cells, deterministic lateral displacement (DLD) devices, and Integrated POC systems [2]. The way of four methods same such as combines isolation, characterization, qualification, self-assembly, and finding inertial balanced. The destination of using urine with that four method is to detection cancer cells and exosomes, tumor cells, diabetic, escheria coli, etc cause urine contains several types of cells.

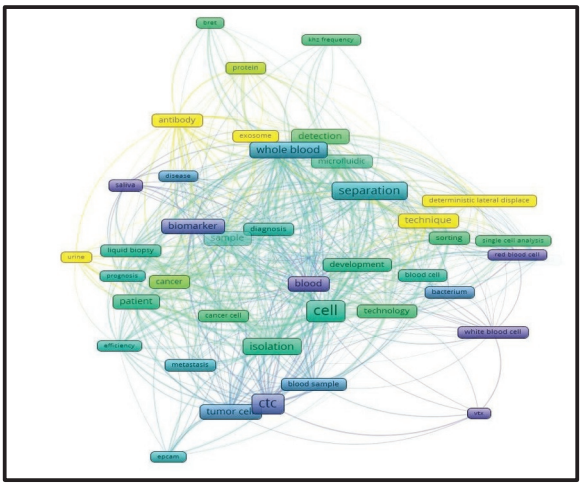

Figure 3. Overlay visualization of Microfluidic device.

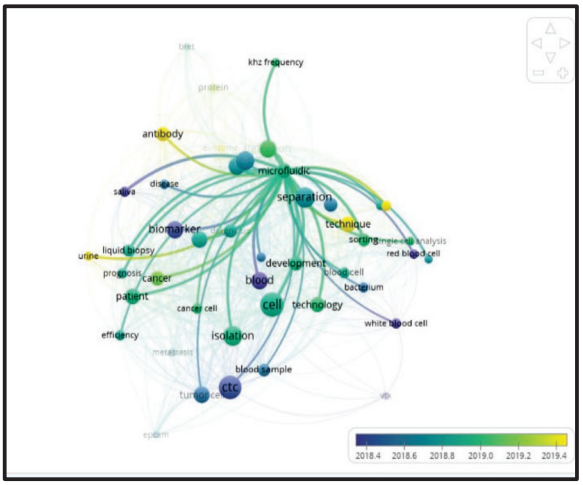

Figure 4. Sub-division overlay visualization of Microfluidic device.

The data visualization was obtained through the analysis of 33 selected and filtered data using the PRISMA method. The displayed data visualization represents the most recent research conducted. In Figure 4, the varying shades of color indicate the time elapsed since the research was conducted. Darker colors indicate studies conducted in 2018, while brighter colors (yellow) indicate more recent research conducted in 2019. The next step would be to conduct an analysis focusing on the topic of microfluidics, specifically addressing the existing research gap in microfluidic separation studies. The analysis reveals a noticeable gap between microfluidic separation and research concerning urine samples. A recommendation for future research would be to explore the relationship between microfluidic separation and urine as a specimen. It is widely known that urine can serve as a valuable specimen for various diagnostic purposes, including drug testing, diseases like diabetes, tumors, and even cancer [23]. Therefore, considering the advancements in current technology, investigating the utilization of urine as a specimen for microfluidic separation holds significant potential.

4.3 Future recommendations

The analysis conducted in this research employed two distinct methods, namely scientific literature analysis and bibliometric analysis. Each analysis method has its own merits, assisting researchers in providing various recommendations for future research on urine as a specimen for detecting various conditions, ranging from drug testing to early diagnosis of diseases. Considering the rapidly advancing technology, particularly in the medical field, and the growing public awareness of health, further research on the relationship between microfluidic separation and the use of urine as a specimen needs to be intensified in the future.

Currently, urine is infrequently utilized as a specimen in microfluidic separation. Blood and saliva are the most commonly employed specimens in microfluidic separation. Further insights into the topic related to the research gap can be obtained from previous papers in the preceding sections. There is also a significant potential in exploring the use of urine as a specimen in microfluidic separation. As highlighted in a study titled "The isolation of tumor cells from urine with localized prostate cancer can be achieved using inertial microfluidics," we can know that there is a potential of urine test as an early diagnosis tool for various diseases.

Based on these considerations, there are still ample opportunities and potential for research by employing microfluidic separation to further investigate and broaden our understanding of urine as a specimen.

5. Conclusion

This paper proposes a systematic literature review and bibliometric analysis to conduct an analysis of microfluidic separation. The papers analyzed were obtained through a literature search from the Scopus Database with the keywords "Microfluidic", "Blood", and "Separation". Several inclusion and exclusion criteria were also considered. Through a systematic search process, researchers identified 13 core papers that had high relevance to the keywords and met the required criteria. The 13 selected papers were then summarized and discussed in the form of a systematic literature review to provide readers with a brief understanding. In addition, a bibliometric analysis was carried out to reveal research and publication gaps on urine as a specimen of microfluidic separation. The results reveal the study of microfluidic blood separation using urine as a specimen could be able to detect various diseases (diabetes, tumor, even cancer).

There is also useful information regarding the use of the microfluidic blood cell division method which is the most widely used in microfluidic blood separation research. In terms of cell separation methods using microfluidic, the passive method has the most attention from microfluidic blood separation researchers. Based on the bibliometric results, urine is one of the topic an that has not been widely researched as a research object in microfluidic blood separation. As a step forward, the researchers encourage further exploration and research regarding the safety use of the microfluidic blood separation with passive method by providing several

papers as initial references. We believe that this research can enable future researchers to produce microfluidic blood separation with a passive method using 3D printing which is more economical which is expected to support the development of the health industry.

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