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Application of droplet digital PCR in infectious diseases: A bibliometric analysis

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Abstract: *Infectious diseases represent a significant burden on global public health. Digital PCR (dPCR) has emerged as a novel tool for diagnosing prevalent infectious disease pathogens. However, there is currently a lack of bibliometric analyses that systematically examine the full scope of this research area. To address this gap, we have identified the research hotspots and emerging trends in the application of dPCR for infectious diseases to analyze the current landscape and future directions of digital PCR applications in this field. This study examines the application of digital PCR in infectious diseases, utilizing literature from the Web of Science Core Collection covering the period from June 2014 to June 2024. Bibliometric analyses were performed using VOSviewer and CiteSpace. 496 documents were included in this study, revealing that the publication trend in this field over the past ten years has undergone three distinct phases: a slow rise, a rapid increase, and a subsequent slow decline. A core group of journals focusing on microbiology-related topics has begun to emerge in this field; however, a core group of authors has yet to be established. The reference titled "Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients" is the most frequently cited, and the high-frequency keywords include digital PCR and SARS-CoV-2. This bibliometric analysis represents the first comprehensive summary of digital PCR in infectious disease research. The study identifies key hotspots and development trends of digital PCR applications in this field while also providing an in-depth analysis of the researchers, research institutions, and emerging hotspots and frontiers associated with digital PCR. This work offers insights for relevant researchers and future investigations.*

Keywords: *Digital PCR, Infectious diseases, Bibliometric analysis*

1. Introduction

Infectious diseases represent a significant challenge to global public health, with persistent high morbidity and mortality rates that pose a substantial threat to human health. The continuous advancement of medical technology has enhanced the importance of rapid etiological diagnosis and early, accurate prognosis, which are crucial for improving patient outcomes[1] . Digital PCR (dPCR), particularly Droplet Digital PCR (ddPCR), has emerged as a promising diagnostic tool for pathogens. Its growing popularity can be attributed to several significant advantages, including high sensitivity, high accuracy, and independence from standard curves. This technology has garnered considerable attention from both academic researchers and clinical practitioners[2]. Despite the gradual increase in research focused on applying digital PCR (dPCR) in infectious diseases, particularly regarding its diagnostic value, systematic bibliometric analyses in this area still need to be improved. This study employs bibliometric methods to systematically analyze the relevant English literature published in the Web of Science Core Collection database from June 2014 to June 2024. The aim is to elucidate the current status, hotspots, and emerging trends in research on digital PCR (dPCR) in infectious diseases. This study employs a combination of quantitative and qualitative analysis methods to investigate the research trends, primary contributors, key research institutions, and notable research hotspots related to digital PCR (dPCR) technology in the diagnosis of infectious diseases. The visual analysis conducted using VOSviewer and CiteSpace software aims to offer researchers in this field a comprehensive perspective. This analysis also seeks to establish a theoretical foundation that supports the application of digital PCR (dPCR) in infectious diseases, including pathogen detection, prediction of patient

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severity and outcomes, and research on drug resistance genes.

2. Methods

2.1 Data Acquisition and Search Strategy

All data in this article are sourced from the Web of Science (WOS), one of the most widely utilized databases in academic and bibliometric research. The search terms were set to ((((TS=(dpcr)) OR TS=(digital PCR)) OR TS=(digital polymerase chain reaction)) AND ((((((((((TS=(Infection)) OR TS=(microorganism)) OR TS=(pathogen)) OR TS=(bacterial)) OR TS=(viral)) OR TS=(fungi)) OR TS=(actinomycetes)) OR TS=(rickettsia)) OR TS=(mycoplasma)) OR TS=(Chlamydia)) OR TS=(Spirochaeta)) OR TS=(parasites))) AND LA=(English). The search period spans from June 2014 to June 2024, resulting in a total of 2017 English documents. Two researchers subsequently removed duplicate documents, conference abstracts, editorial materials, book chapters, and documents unrelated to the application of digital PCR in infectious diseases. Ultimately, 496 English documents were included and exported in plain text format for further analysis. To mitigate potential bias from daily updates to the database, we downloaded all data on June 15, 2024.

2.2 Data Extraction

Two researchers, Hou Xueping and Zhang Jing, systematically extracted data from all included studies. The extracted data encompassed the title, abstract, keywords, references, source journal, publication date, total number of citations across all databases, author affiliation, country, and journal impact factor (IF). Institutions and countries are listed according to the corresponding author. The IF is derived from the Journal Citation Report (JCR) 2022 to reflect academic impact accurately. Two researchers from the research team (BBB and CCC) analyzed and screened the keywords, excluding terms that lacked significant correlation and merging synonyms (e.g., pcr and PCR). In cases of disagreement, a third investigator (Xiao Linlin) was consulted.

2.3 Data Analysis

VOSviewer, developed by Nees Jan van Eck and colleagues, is primarily utilized for analyzing bibliometric networks through graphical representation[3]. CiteSpace is a Java-based application for analyzing and visualizing the scientific literature coverage and research boundaries of a specific field or area of knowledge over time. Use techniques such as econometrics, co-event analysis, and cluster analysis[4]. We used VOSviewer (version 1.6.20) and CiteSpace (version 6.3.1) to analyze the usage of journals, authors, countries, affiliations, and keywords in pathogen detection.

3. Results

3.1 Temporal distribution map of the literature

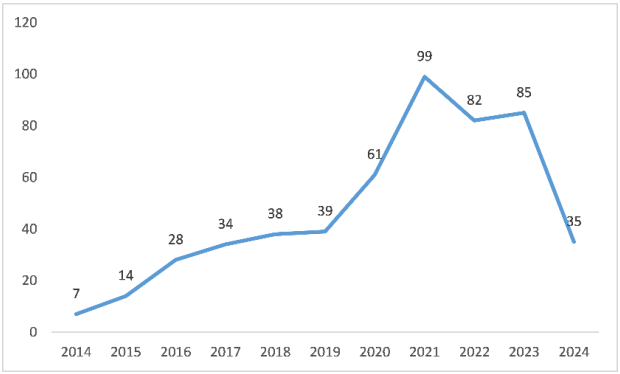

Figure 1: Annual change in the number of documents.

A total of 2,017 documents were initially retrieved, from which conference abstracts, news reports, and other papers unrelated to the topic were excluded. Ultimately, 496 English documents were selected for analysis. The publication status of articles over the past decade is illustrated in Figure 1,

ISSN 2618-1584 Vol. 6, Issue 10: 18-27, DOI: 10.25236/FMSR.2024.061003

which delineates three distinct stages: the initial stage of slow development (2014-2018), the rapid growth stage (2019-2021), and the slow decline stage (2022 to the present). The number of published articles increased from 7 in 2014 to 92 in 2021. Notably, the average annual number of publications during the initial stage was 23.6, whereas, in the rapid growth stage, the annual number of articles published reached an average of 63.

3.2 Distribution of countries

A statistical analysis of the publication status of each country was conducted using documents compiled from the Web of Science Core Collection database. As shown in Table 1, the results indicate that the literature is predominantly concentrated in countries such as the United States, China, and Italy. The United States and China published 173 and 118 articles, respectively, accounting for 34.88% and 23.84% of the total publications. These two countries are significantly ahead of their counterparts, underscoring their central role in research within this domain. Furthermore, Australian publications demonstrated exceptional citation performance, with 29 papers garnering 979 citations, yielding an average of 33.76 citations per paper. Furthermore, we utilized VOSviewer software to generate a country-label view (Overlay visualization), as illustrated in Figure 2. Notably, the United States and the United Kingdom pioneered research within this field. The United States has established extensive cooperative relationships with several countries, including China, the United Kingdom, Australia, and Canada, and its connection to China is remarkably robust, indicating a notably close collaborative relationship between the two nations.

Table 1: The top 10 countries in the number of publications.

Rank	Country	Documents	Citations	Average Citation
1	USA	173	4584	26.50
2	Peolpes R China	118	2750	23.31
3	Italy	57	1316	23.09
4	England	31	751	24.23
5	France	31	545	17.58
6	Australia	29	979	33.76
7	Canada	21	610	29.05
8	Spain	17	489	28.76
9	Thailand	13	379	29.15
10	Switzerland	12	392	32.67

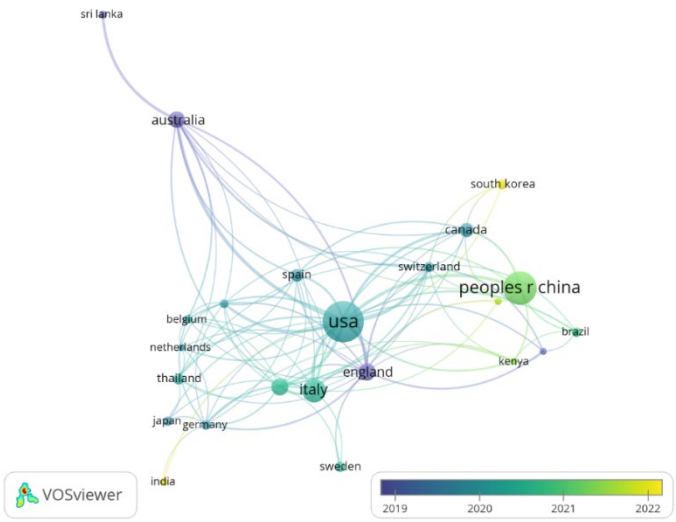

Figure 2: Overlay visualization of countries distribution.

3.3 Distribution of organization

Table 2 presents the statistics of the top 10 institutions listed in the Web of Science Core Collection database. Most of these institutions are higher education establishments that have published relevant

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papers. The University of California leads with the highest output, having published 18 related articles. The University of Washington and the University of Milan are tied for second place, each with 15 published articles. Fudan University in China ranks fifth, contributing 11 related articles.

Table 2: The 10 most published organizations.

Rank	Organization	Documents	Citations	Average Citation
1	University of California, San Francisco	18	715	39.72
2	University of Washington	15	447	29.80
3	University of Milan	15	292	19.47
4	Fred Hutchinson Cancer Research Center	14	486	34.71
5	The London School of Hygiene & Tropical Medicine	14	231	16.50
6	Johns Hopkins University	13	459	35.31
7	Fudan University	11	64	5.82
8	University of California, San Diego	11	215	19.55
9	National Institute of Neurological Disorders and Stroke (NINDS)	10	193	19.30
10	QIMR Berghofer Medical Research Institute	9	366	40.67

3.4 Authors analysis

An analysis of the authors featured in the literature reveals the presence of prominent scholars within the field. Table 3 presents the top ten authors ranked by the number of published articles. The five authors with the highest publications in this research domain are Jerome Keith, Telwatte Sushama, Yukl Steven, Jacobson Steven, and Roberts Chrissy. Notably, the author with the highest average citations per article is Cai Pengfei, who has an average of 51.14 citations.

Table 3: The 10 most published authors.

Rank	Author	Documents	Citations	Avaerage Citation
1	Jerome Keith R.	10	386	38.60
2	Telwatte Sushama	10	324	32.40
3	Yukl Steven a.	9	334	37.11
4	Jacobson Steven	9	193	21.44
5	Roberts Chrissy H.	9	187	20.78
6	Mcmannus Donald p.	8	362	45.25
7	Wong Joseph p.	8	363	45.38
8	Alteri Claudia	8	167	20.88
9	Cai Pengfei	7	358	51.14
10	Gianella Sara	7	306	43.71

3.5 Distribution of journals

Table 4: The 10 most published journals.

Rank	Source	Documents	Citations	Avaerage Citation
1	Scientific Reports	17	296	17.41
2	Microbiology Spectrum	16	61	3.81
3	Plos One	14	380	27.14
4	Journal of Virological Methods	12	248	20.67
5	Journal of Clinical Virology	12	229	19.08
6	Journal of Clinical Microbiolgy	11	384	34.91
7	Frontiers in Cellular and Infection Microbiolgy	11	188	17.09
8	Frontiers in Microbiolgy	11	143	13.00
9	Journal of Virology	10	344	34.40
10	Viruses-basel	10	81	8.10

Most papers in this research field are published in microbiology-related journals (as shown in Table 4). "Scientific Reports" and "Microbiology Spectrum" have published over 15 papers. Among the top

ISSN 2618-1584 Vol. 6, Issue 10: 18-27, DOI: 10.25236/FMSR.2024.061003

10 journals by publication volume, the "Journal of Clinical Microbiology" boasts the highest number of citations per article, averaging 34.91 citations. Additionally, the "Journal of Virology" has an average of 34.40 citations per article, indicating that research published in these two journals has garnered significant attention within the field.

3.6 The 10 most frequently cited publications

This study includes nearly 500 documents, of which the 10 most cited articles are presented in Table 5. Among these, four articles focus on applying digital PCR in patients with SARS-CoV-2 infection, all about the etiological diagnosis of COVID-19 in infected individuals using droplet digital PCR.

Table 5: The top 10 cited publications.

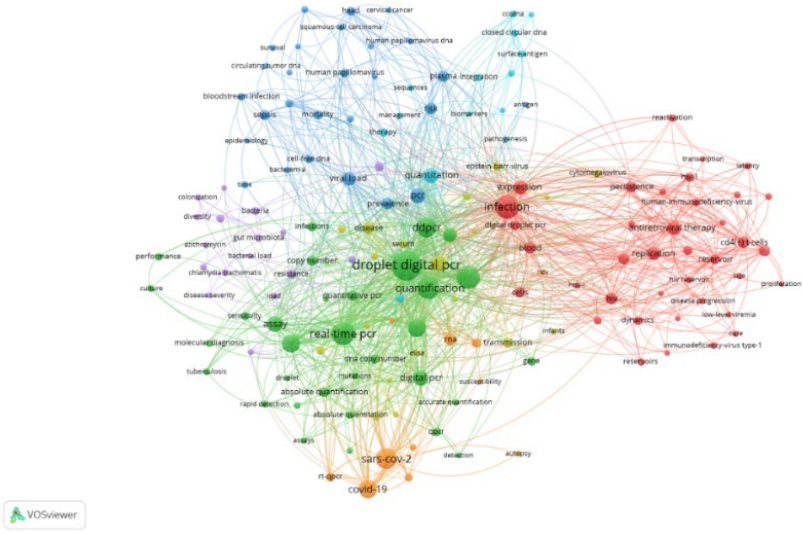
Rank	Title	Author	Year	Citations	IF
1	Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients	Fengting Yu	2020	444	11.8
2	Droplet microfluidics for microbiology: techniques, applications and challenges	Tomasz S. Kaminski	2016	303	6.1
3	ddPCR: a more accurate tool for SARS-CoV-2 detection in low viral load specimens	Tao Suo	2020	288	13.2
4	HIV latency in isolated patient CD4 T cells may be due to blocks in HIV transcriptional elongation, completion, and splicing	Steven A Yukl	2018	211	17.1
5	Advances in digital polymerase chain reaction (dPCR) and its emerging biomedical applications	Lei Cao	2017	196	12.6
6	Advances in the Diagnosis of Human Schistosomiasis	Kosala G A D Weerakoon	2015	193	19
7	Lung Microbiota Predict Clinical Outcomes in Critically Ill Patients	Robert P. Dickson	2020	187	24.7
8	Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19	Jesús F Bermejo-Martin	2020	164	8.8
9	Sensitivity assessment of droplet digital PCR for SARS-CoV-2 detection	Luca Falzone	2020	148	5.7
10	Digital PCR analysis of circulating nucleic acids	Irena Hudecova	2015	139	2.5

3.7 Keywords analysis

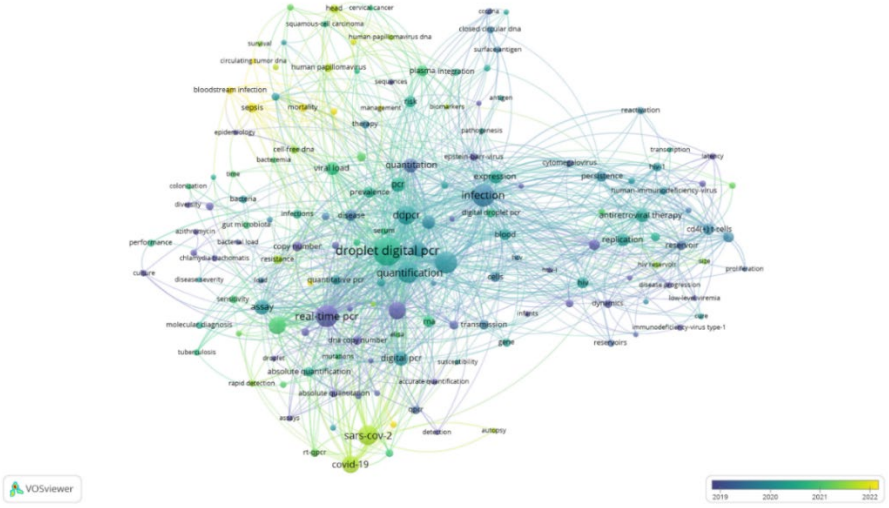
Keywords are a crucial component of this article, as they effectively represent the topics within related research fields, highlight current research hotspots, and indicate potential future research directions. We utilized VOSviewer software to perform a keyword cluster analysis, visually presenting the clustering results through network and tag views showed in Figure 3. In these visualizations, distinct colors denote different clustering categories.

In the network visualization, we identified five primary clustering themes: Cluster 1 (red) emphasizes research on the pathophysiological mechanisms of infection; Cluster 2 (blue) concentrates on treatment options for infectious diseases; Cluster 3 (green) highlights technologies associated with digital PCR; Cluster 4 (orange) investigates the issue of SARS-CoV-2 infection; and Cluster 5 (purple) pertains to the types of samples utilized in PCR testing. The data reveal that the keywords 'Droplet Digital PCR,' 'Infection,' 'SARS-CoV-2,' and 'Real-Time PCR' are frequently encountered in this field. We also employed Citespace software to perform a timeline analysis of keywords (as shown in Figure 4), indicating that recent research hotspots include Digital PCR technology, bloodstream infections, HIV, HBV, trachoma, and HPV. By integrating the label view with the timeline view, we can reasonably predict that future research innovations may focus on the in-depth exploration of ddPCR technology for the detection and absolute quantification of pathogens associated with bloodstream infections, as well as HBV and HIV infections.

ISSN 2618-1584 Vol. 6, Issue 10: 18-27, DOI: 10.25236/FMSR.2024.061003



3a: Network Visualization of keywords.



3b: Overlay visualization of keywords.

Figure 3: Co-occurrence of keywords in documents related to dPCR in infectious diseases research.

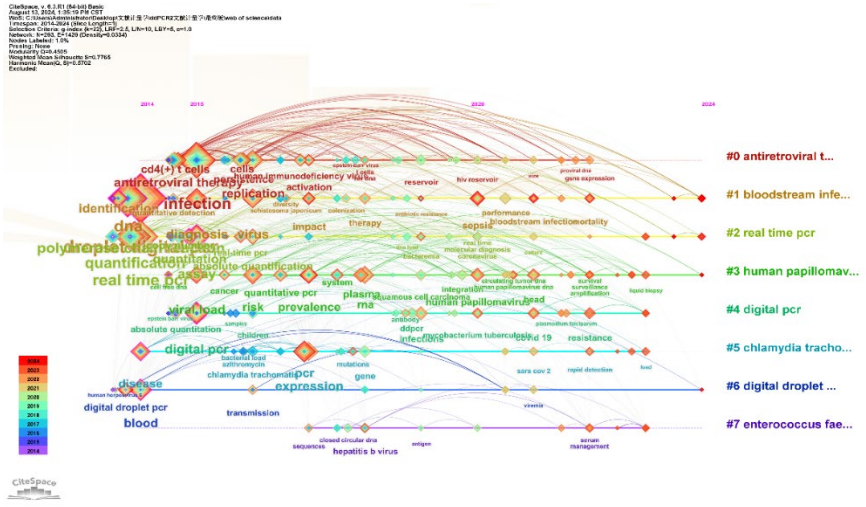


Figure 4: Timeline view of co-occurring keywords map of dPCR in infectious diseases research.

ISSN 2618-1584 Vol. 6, Issue 10: 18-27, DOI: 10.25236/FMSR.2024.061003

3.8 Keywords with citation bursts

To enhance our understanding of the research frontiers and development trends of digital PCR (dPCR) in the context of infectious diseases, we utilized CiteSpace to perform a keyword emergence analysis. The Figure 5 illustrates that the keyword with the highest burst intensity is 'real-time PCR.' The emergence intensities of the keywords 'copy number' and 'DNA copy number' are comparable, measuring 3.65 and 3.63, respectively, with both keywords exhibiting the most extended emergence duration. Additionally, the keywords 'resistance' and 'mortality' emerged in 2022 and have continued, suggesting that research on these topics may warrant ongoing attention.

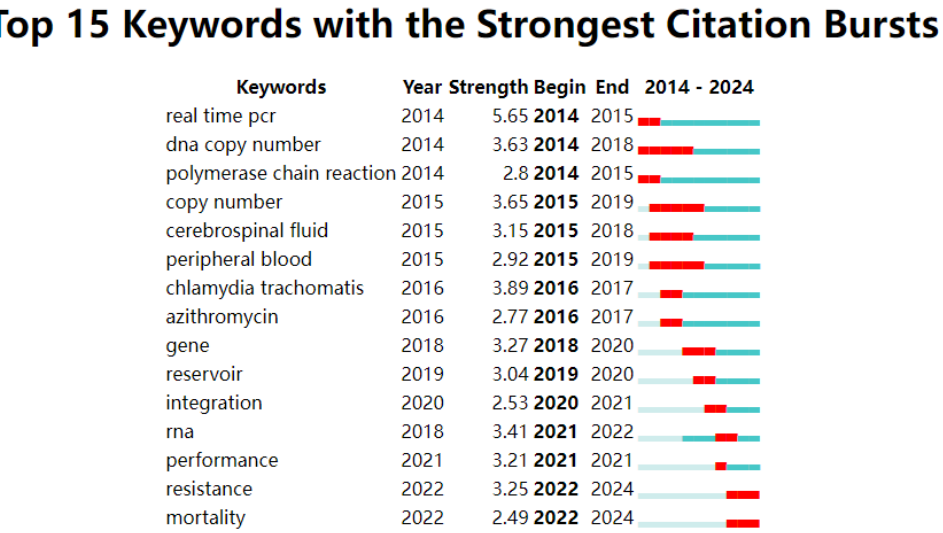


Figure 5: Top 15 keywords with the strongest citation bursts.

4. Discussion

Digital PCR (dPCR) detection technology, characterized by its high sensitivity, accuracy, and capability for absolute quantification, has demonstrated significant potential and advantages in molecular diagnostics, including applications such as liquid biopsy for cancer, non-invasive prenatal testing, and infectious disease diagnosis[5]. Following the outbreak of the COVID-19 pandemic at the end of 2019, dPCR leveraged these strengths to reveal its unique value across various studies, including virus detection, quantification, disease monitoring, and new drug evaluation, garnering considerable attention from researchers[6]. In recent years, a substantial body of research has investigated its exceptional performance in diagnosing infectious diseases, particularly concerning pathogens[7]. However, the extent and specific depth of its application in infectious diseases still need to be determined. This article aims to analyze the application of digital PCR in infectious diseases through bibliometric methods, providing researchers with a comprehensive perspective, highlighting research hotspots, and identifying potential research directions.

4.1 Publication Analysis

The publication trend chart indicates that over the past decade, the volume of publications on digital PCR in infectious diseases has generally increased, with a notably accelerated growth rate observed since 2019. Articles published between 2019 and 2023 represent 75.76% of the publications from the past ten years. This surge is closely linked to the gradual maturation of digital PCR technology and the global circumstances surrounding the COVID-19 outbreak that began in late 2019.

4.2 Research Hotspots in the Application of Digital PCR in Infectious Diseases

4.2.1 Early Diagnosis of Infectious Diseases

Digital PCR technology, particularly droplet digital PCR, offers significant diagnostic advantages, including high sensitivity, rapidity, and reproducibility. This capability allows for the absolute quantification of low concentrations of free nucleic acids without needing external calibration curves[8].

ISSN 2618-1584 Vol. 6, Issue 10: 18-27, DOI: 10.25236/FMSR.2024.061003

In infectious diseases, this technology is especially notable for its role in early diagnosis, particularly for viral infections, underscoring its critical importance. A thorough literature review reveals that over the past decade, approximately 66.13% of the studies have concentrated on diagnosing viral infections, while 17.94% have addressed bacterial infections. Furthermore, around 40 publications investigate the application of this technology in the early diagnosis of other infectious diseases, including fungal and parasitic infections.

In the early diagnosis of viral infections, digital PCR is extensively utilized to detect SARS-CoV-2 rapidly. Its advantages include fast detection speed, high sensitivity, strong specificity, and tolerance to enzyme inhibitors[9]. Among the more than 400 articles included in our review, 109 discussed the application of digital PCR in COVID-19 diagnostics, with approximately 70% focused on diagnostic studies. Furthermore, the early diagnosis of the incubation period following HIV infection is also a significant research focus, with about 55 related publications. Digital PCR demonstrates advantages over traditional methods (such as culture and serological testing) in bacterial infections, particularly in diagnosing Mycobacterium tuberculosis infection[10]. Digital PCR technology offers a rapid, non-invasive diagnostic method that does not require invasive procedures to obtain samples. This is especially crucial for early asymptomatic latent pulmonary tuberculosis and extrapulmonary tuberculosis patients[11]. Traditional diagnostic methods in parasitology primarily rely on microscopic examination. While this approach is simple and cost-effective, it has limitations in reproducibility, specificity, and sensitivity. In contrast, digital PCR technology exhibits high sensitivity, specificity, and reproducibility, indicating significant potential for application in diagnosing parasitic infections. This technology is predominantly focused on the early diagnosis of Schistosoma and Plasmodium infections[12].

4.2.2 The treatment of infectious diseases

Digital PCR distributes samples into many independent micro-reaction units during detection, allowing for only one or a minimal number of target molecules in each unit. This extreme dilution ensures the independence of each reaction unit, effectively compensating for the low-abundance viral DNA that may be overlooked by traditional methods[13]. This aspect is particularly crucial in the early diagnosis of viral infections. Moreover, it aids researchers in investigating the pathophysiological mechanisms underlying virus latency and reactivation within the body. Such insights are vital for understanding the latent mechanisms of HIV and other retroviruses, and they also provide technical support for the exploration of new therapies aimed at eradicating latent infections of HIV and other retroviruses[14].

Treatment failure in infectious diseases is closely linked to drug resistance. As an exact quantitative nucleic acid detection and analysis technology, digital PCR (dPCR) can identify specific pathogens' resistance genes before initiating anti-infective treatment, which is essential for rationally selecting anti-infective drugs. Currently, most research on the detection of drug-resistant genes focuses on mutations associated with antiviral drug resistance (e.g., oseltamivir resistance genes) and mutations related to anti-tuberculosis drugs (e.g., rifampicin and isoniazid resistance genes) [15,16]. If resistance genes are identified, it allows for the early substitution or addition of alternative anti-infective drugs during treatment. Conversely, when only susceptibility alleles are detected, the anti-infective treatment regimen should be simplified to minimize side effects and enhance patient compliance. Through these strategies, the efficacy of treatment for infectious diseases can be significantly improved[17,18].

Digital PCR technology can detect pathogens at exceptionally low titers, enabling the monitoring of pathogen numbers during anti-infective treatments. As Huang Jingtao et al. [19] demonstrated, digital PCR is utilized in real-time to monitor the copy number of covalently closed circular DNA (cccDNA) during antiviral treatment, thereby evaluating its effectiveness. This technology serves as a promising strategy for assessing anti-infective treatments. However, it can also facilitate timely adjustments to treatment plans by tracking pathogen copy numbers, optimizing treatment strategies, and ultimately enhancing treatment success rates.

4.2.3 Predicting the severity of the disease

The early and accurate prognosis prediction for infected patients is crucial for developing personalized treatment strategies. Digital PCR can precisely measure the DNA content of microbial cell-free nucleic acids in patients with low viral loads, thereby effectively predicting the severity and prognosis of infections. Jiang Sen et al. highlighted that digital PCR can be an early warning method for emergency patients at risk of progressing to sepsis[20]. Furthermore, meta-analysis has demonstrated that digital PCR can quantify SARS-CoV-2 RNA levels in hospitalized patients, indicating its emerging prognostic value as a complementary or alternative tool for assessing SARS-CoV-2 viral infection

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levels[21].

5. Conclusion

This study employed VOSviewer and CiteSpace to analyze the literature concerning the application of digital PCR in infectious diseases, utilizing the Web of Science core database. The analysis clearly and intuitively illustrates the trends in research and identifies potential research hotspots in recent years. This serves as a valuable reference for our country to explore further the application of digital PCR in the field of infectious diseases and to establish future research directions. Previous studies have indicated that digital PCR is a promising tool for pathogen identification, severity assessment, prognosis, treatment guidance, and analysis of the host response to infection in the blood, owing to its high sensitivity, specificity, and rapid processing time[22]. Future research should prioritize the accuracy and efficiency of pathogen diagnosis and address the challenge of false positives. Additionally, practical studies are necessary to investigate the application of digital PCR in treating infectious diseases and its effects on patient prognosis.

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