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Review Article

Exosomes: A Fluid Biopsy Source for Clinical Interventions of Noncommunicable Diseases Treatment: A Review

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Abstract

Introduction: The beginning of exosome biosynthesis is marked by the emergence of the initial endosomes through the inward splitting of the plasma cell membrane. This process is facilitated through the endosomal categorization complex essential for transport, which is also involved in the production of different extracellular vesicles. Exosomes are naturally occurring nanosized vesicles found in all bodily fluids and can be successfully extracted from preserved biological materials, while maintaining their structural integrity.

Methods: The articles published recently in high-quality journals (Science Direct, Springer, Institute of Electrical and Electronics Engineers (IEEE), and Taylor & Francis) indexed in various indexing sources such as Scopus, Web of Science, PubMed, Google Scholar, and so on were collected using keywords such as fluid biopsy (FB) exosomes, endosomes, and noncommunicable diseases (NCDs) treatment, new biomarkers, and treatment.

Discussion: In recent years, exosomes have emerged as an exciting option for "FB" that has demonstrated significant potential in the areas of noninvasive medical testing, predictions, as well as tracking responses to therapy for noncommunicable diseases. Nevertheless, specific constraints need to be addressed to expand the application of exosome-based FB as a widely accepted and reliable testing method in typical medical facilities.

Conclusion: This review provides a comprehensive overview of our present understanding of exosomes to be an FB method for diagnosing, predicting outcomes, and tracking treatment responses in NCDs. It also discusses the main constraints, innovations in technology, as well as future possibilities of using this application in medical treatment.

Keywords: fluid biopsy, disease progression, diagnosis, treatment response monitoring, healthcare

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1. Introduction

The shift from tissue-based traditional investigations to fluid biopsy (FB) has transformed diagnostic investigations since they are painless, quick, noninvasive, and can be carried out regularly under definite situations, revealing the 'real-time' molecular outline with the fluid activity of an illness. Investigators suggested their importance as biochemical indicators, and the medical scientific profession noticed an alternative for a solid biopsy in the type of circulatory cell-free deoxyribonucleic acid (ccfDNA), as well as circulating tumor cells (CTCs) which were referred to as fluid biopsies [1]. FB has an important benefit over usual tissue biopsy, as it can be less painful for patients and offers significantly, additional, detailed analytical and prognostic data regarding the medical condition before and after therapy. It facilitates sampling for diseases in an extremely easy intrusive or noninvasive manner, reducing the hazards related to using tissues in the sampling procedure while providing continuous monitoring of disease progression as well as therapy effectiveness. Different conventional biopsies and FB techniques can be carried out safely even in severe medical situations. At this point, most of the frequently employed FB methods have employed circulatory cell-free Ribonucleic acid (ccfRNA) and CTCs. Nonetheless, the absence of surface markers as well as a lack of suitable cell-free DNA constitutes two limitations that render those molecules less useful than FB approaches. Medical researchers are currently concentrating on the increasing significance of 'exosomes' in medicinal uses [2]. Exosomes are lipid bilayer vesicles endosomal membrane origination with dimensions that vary from 40 to 150 nm, produced by about all cell sorts in the body's structure, and are found throughout each cell's fluid. These consist of voluntarily generated vesicles that are usually classified as a split of intraluminal vesicles that discharge while multivesicular bodies merge in the plasma membrane interior. Initially, exosomes were believed to eliminate debris from tissues, this notion was reported by several recent investigations [3] which demonstrates further that exosomes serve an important role in intracellular waste elimination and homeostasis. In addition, exosomes serve as an important part in waste management by facilitating cell interaction and activating significant biological reactions in distant cells. Exosomes are associated with a wide range of cellular physiological functions, including immune regulation. Researchers anticipated the deliberate application of exosomes in medical research, taking into consideration both their distinctive features and inherent capabilities [4]. Exosome investigation has led to major progress, offering novel possibilities for identification and treatment of a wide range of fatal illnesses [5]. Researchers are presently looking for many different uses for exosomes in health therapies, including specific drug delivery as well as customized substances. While biomarker discovery represents the most extensively investigated, related to exosomes so far. Exosomes, containing molecular properties of their parenting cells, offer sufficient and accurate data concerning the parent cell [6, 7]. Moreover, since they are regularly generated, they might be the most reliable tool for real-time illness detection, besides assessing reaction to the efficacy of treatment as well as relapse. Exosomes' common and noninvasive character has facilitated their use in usual medical evaluations as well as response monitoring, making them a perfect choice for FB. Recently, the Minimal Information for Studies

of Extracellular Vesicles 2018 (MISEV2018) guidelines encouraged the utilization of prepared phrases like small extracellular vesicles as a substitute for 'exosomes' except its vesicle source can be determined [8]. This review offers the most current comprehension of the uses, boundaries, and exosome-based FB technological advancement in medical evaluation, prognostication, as well as therapeutic reaction monitoring in noncommunicable diseases (NCDs) conditions, along with possible future applications of exosome-based FB processes for medication.

2. Methods

In reviewing NCDs, diagnosis, prediction, and treatment analysis, we looked at the number of publications accessible through various platforms like Science Direct, Springer, Taylor & Francis, and IEEE, as illustrated in Figure **1**. From 2018 to 2023, search queries focused on selective keywords, including FB exosomes, endosomes, noncommunicable disease treatment, new biomarkers, treatment, prognosis, and diagnosis. Each platform produced a variety of articles, such as research articles, review articles, book chapters, and conference papers. The query returned 10,502 articles from different platforms, of which 124 were relevant to the objectives of our research. We chose 60 publications from among them for this review. Figure **1** shows an overview of the investigation's selection method. In reviewing noncommunicable disease treatment analysis, we examined the number of publications accessible through various platforms, like Science Direct, Springer, Taylor & Francis, and IEEE, shown in Figure **2**.

3. Results

3.1. Exosome-based FB in Noncommunicable Diseases

The demand for a developed, extremely quick, and reproducible diagnostics method has prompted investigators to consider exosomes as an improved option for usage in FB. The FB approach depends on the biological origin of biologically active compounds, such as protein, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and biomarkers that are necessary for disease evaluation and therapy. Exosomes have distinctive characteristics that make them ideal for use in FBs, outperforming alternatives such as CTC, cfDNA, and cfRNA. Exosomes are prevalent and continually generated and aggregated in bodily fluids, making them more prevalent compared to ctcDNAs and cfDNAs. Thus, exosomes serve a significant role in expressing greater intratumor diversity over CTCs in instances where a small number of CTCs are discharged, such as brain tumors.

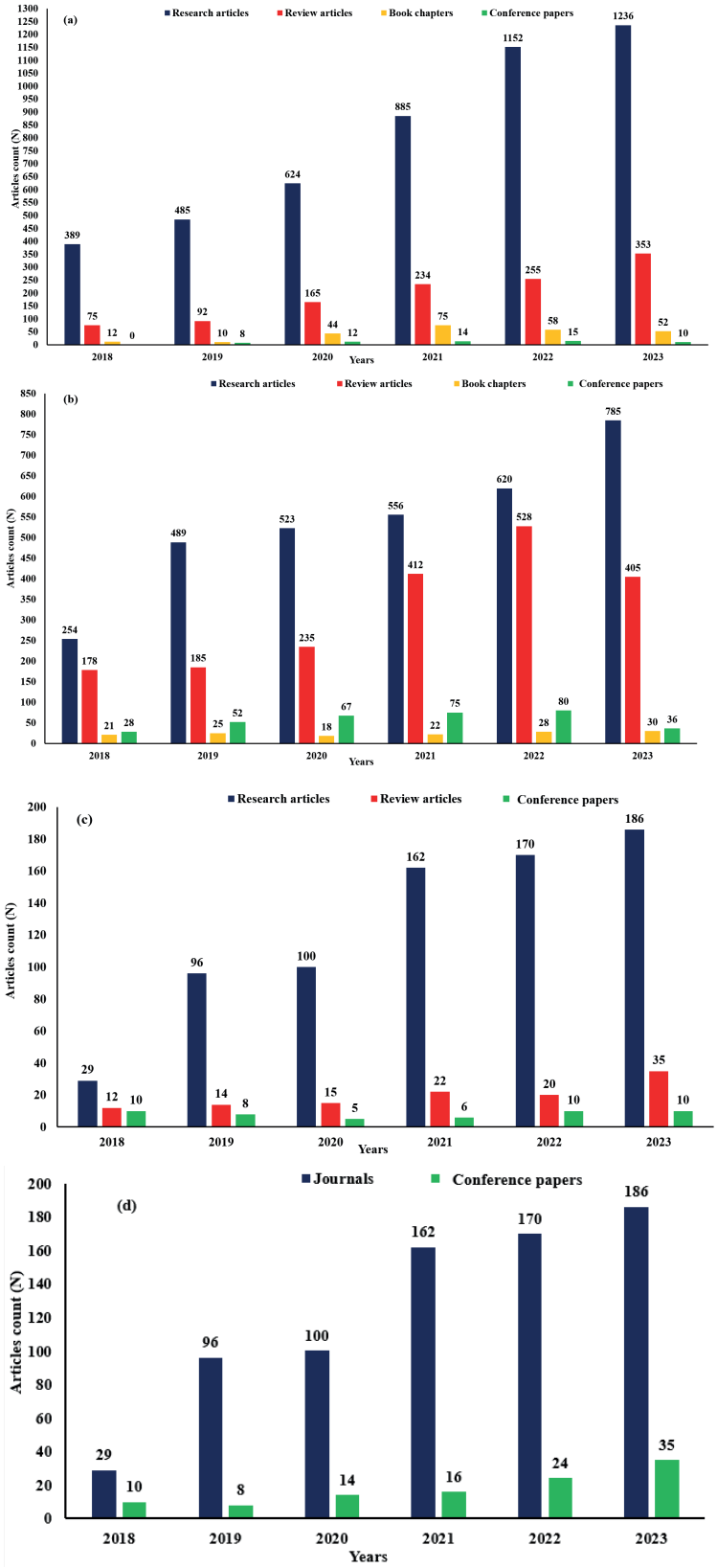

Figure 1: The number of articles related to non-communicable disease diagnosis and treatment were selected from various scientific publishing platforms. **(a)** Science Direct **(b)** Springer **(c)** Taylor & Francis **(d)** IEEE.

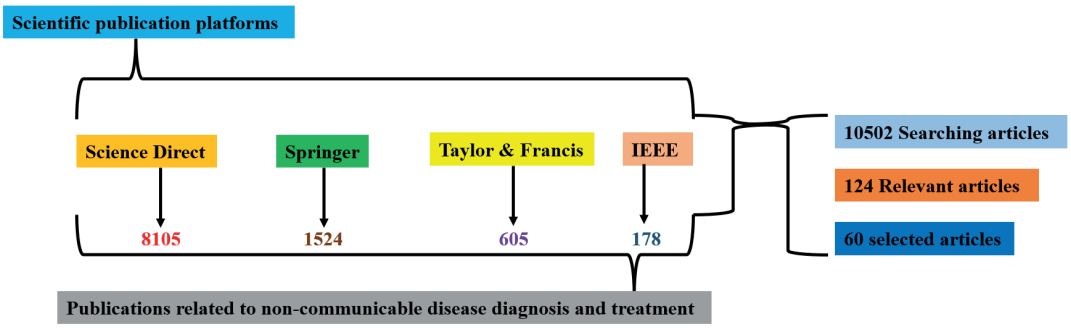

Figure 2: Summary of study selection.

3.2. Diagnosis

Increasing investigations on exosome-related identification as well as assessment of the development of NCDs (diabetes, heart disease, chronic respiratory disease, and cancer) have been presented in extensive publications in this area. Exosomal protein molecules were recently discovered to be diagnostic biomarkers in a variety of cancers, such as colorectal cancer (CPNE3 and glypican-1), ovarian carcinomas (phosphatidylserine), renal cell carcinoma, lung cancer (tetraspanin 8, CD151, and CD171), pancreatic cancer (glypican-1), breast cancer (CD82), as well as cholangiocarcinoma. Barrachina et al., found 6 exosomal proteins (platelet glycoprotein Ib alpha chain, apolipoprotein C-III, apolipoprotein D, complement C1q subcomponent subunit A, complement C5, and platelet basic protein) as biomarkers for the prompt identification of cardiac infarction [9]. Furthermore, exosomal proteins are linked to early detection of pregnancy problems like intrauterine growth restriction and congenital obstructive nephropathy. Researchers discovered hemopexin and exosomal Tetraspanin-1 in urine from recipients of kidney transplants as effective biomarkers in the preliminary identification of acute rejection. A proteomics study on urinal exosomes in diabetic renal failure patients revealed a collection of 3 proteins (VDAC1, MLL3, and AMBP) that could be used to diagnose and monitor the progression of the disease. Exosomal DNA also possesses great promise for diagnosis of a variety of diseases. Several studies provided insight on the function of miRNAs as diagnosing markers. Plasma-based exosomal miRNA has recently been studied as an alternative screening biomarker for a variety of malignancies, such as epithelial ovarian, gall bladder carcinoma, non-small cell lung cancer (NSCLC), cholangiocarcinoma, bladder cancer, as well as breast cancer. Bejleri et al., discovered that serum-based brain-specific miR-124 along with miR-9 could play a predictive function in the identification along with evaluation of injury in acute strokes caused by ischemic stroke [10]. Likewise, urinary exosome (miR-146a) was identified as an intriguing marker for investigating early kidney damage in hypertension. Exosomal miRNAs are additionally used to diagnose pregnant conditions such as pre-eclampsia, hypertension, and congenital obstructive nephritis. Exo-miRNAs may also have an essential function in assessing acute rejection following renal and cardiac transplantation. A few investigations also point to the probable function of serum-based exosomal miRNAs

in the identification of eye disorders such as age-associated metastatic uveal malignancies and macular degeneration. A few investigations have shown that, in addition to miRNAs, the long noncoding RNAs may be useful for prognosis. Wu et al., discovered that the long noncoding RNA could be used as a bloodstream biomarker for Alzheimer's disorder [11]. Exosomal genetic material, like RNAs, has emerged as a desirable target for cancer screening. Following the finding that exosomes possess exosome-based FB and double-stranded DNA, has emerged as a substitute for traditional mutation-based diagnostic techniques, relying on abnormal cellular DNA for identification. Finding the Kristen Rat Sarcoma (KRAS) abnormality in exosomal DNA could function as a useful diagnostic biomarker for pancreatic cancer in its early stages. Earlier and accurate diagnoses can decrease cancer victim death while also increasing the recovery rates. Table **1** lists contemporary clinical investigations on exosomes as markers for different illnesses, their origin, and functional purposes.

Table 1: Selective studies reported about the FBs tool-based exosomal biomarkers for NCDs diagnosis.

NCDs FB sample	Biomarkers	NCDs	Reference
Plasma	lncRNA BACE1-AS	Alzheimer's disease	[28]
Serum	miR-885-5p, miR-486-5p, and miR-626	Age-related macular degeneration (AMD)	[29]
Plasma and serum	Exo-protein CD82, miR-21, and miR-1246	Breast cancer	[30]
Urine	Exo-miRNAs	Bladder cancer	[31]
Plasma and serum	Exosomal CPNE3 and lncRNA	Colorectal cancer	[32]
Serum	Exo-proteins	Cholangiocarcinoma	[33]
Urine	Exo-proteins	Diabetic nephropathy	[34]
Plasma	miR-210	Pregnancy hypertension	[35]
Urine	Tetraspanin-1, exo-miRNAs, and Hemopexin	Kidney transplantation	[36]
Urine	Exosome miR-146a	Albuminuria and renal injury	[37]
Plasma	Exo-proteins	Myocardial infarction	[38]
Plasma	miR-486-2-5p, and miR-486-1-5p	Pre-eclampsia	[39]
Serum	miR-142-3P	Heart disease	[40]
Urine	Exosome gene expression assay	Prostate cancer	[41]
Plasma	Exo-proteins, exo-miRNA, and EGFR T790M	Lung cancer	[21]

3.3. Prognosis

In recent times, many exosomal proteins have been studied as possible prognostic biomarkers for malignancy along with other NCDs. Pancreatic duct adenocarcinoma exosomes with elevated levels of the migrating inhibiting factor (MIF) suggest the emergence of pancreatic ductal adenocarcinoma (PDAC) hepatic metastases. Tumor-derived exosomes were identified as a critical biomarker source for improved prognosis as well as progression of disease evaluation because they can be easily extracted from bodily fluids such as saliva, blood, as well as urine. Table **2** shows a few recently discovered exosomal

Table 2: Selective studies reported about the FBs tool-based exosomal biomarkers for NCDs prognosis.

NCDs FB sample	Biomarkers	NCDs	Reference
Plasma	Exo-proteins	Alzheimer's disease	[42]
Serum	miR-222	Breast cancer	[43]
Saliva	Exosomal chimeric GOLM1-NAA35 RNA	Esophageal carcinoma	[44]
Serum/plasma	miR-548c-5p, miR-19a, miR-141-3p, miR-92a-3p, miR-375, and miR-17-5p	Colorectal cancer	[21]
Plasma	Exo-proteins ficolin 3	Abdominal aortic aneurysm	[45]
Serum	Exo-proteins	Heart	[46]
Serum	Exo-proteins	Parkinson's disease	[47]
Plasma	PLAP and CD63	Gestational diabetes mellitus	[48]
Serum	Exo-miRNA	Multiple sclerosis	[49]
Serum	FL-1 exo-RNAs	Lung cancer	[50]
Serum	S100B, miRNA-125b and MIA	Melanoma	[51]
Plasma	Exo-proteins	Ovarian cancer	[52, 53]
Saliva	Exosomal chimeric GOLM1-NAA35 RNA	Esophageal carcinoma	[44, 54, 55]
Urine	ITGB1 and ITGA3	Prostate cancer	[53, 56, 57]
Plasma	Exosomal SOCS2-AS1	Coronary artery disease	[54, 58, 59]

biomarkers of prognosis consisting of KRAS protein, CD133, programmed death ligand 1 (PD-L1), and c-MET93, for pancreas malignancy (miR-548c-5p: miR-miR-375 and 141-3p), colon cancer (miR-19a: miR-17-5p and miR-92a-3p); miR for breast cancer, lung cancer (FL-11 exo-RNAs99); head and neck cancer (PD-L1), and so on. Exosome-based biomarkers are being extensively studied in illnesses besides malignancy, such as neurological conditions, pregnancy illnesses, as well as heart disease. Blood exosomes created by neurons have been identified as having substantial proteins related to several neurological disorders, such as Alzheimer's, Prion, and Parkinson's disorders. A research team discovered that the quantity of neuron-based exosomal proteins like ubiquitinylated proteins, cathepsin D, heat shock protein (HSP 70), and lysosome-associated membrane protein- 1, have changed among people, years before the first signs of Alzheimer's syndrome. Likewise, Abdel-Haq found that the ratio of P-pan-tyrosine-IRS-1 and P-serine312-IRS-1 in bloodstream exosomes produced by neural cells might have predicted the first signs of Alzheimer's disorder in individuals with Type-II diabetes, up to 10 years before the illness manifested [12]. The miRNA biomarkers and exosomal proteins for predicting certain heart conditions, including myocardial infarction (MI) and heart failure, were also studied. Plasma ficolin-3 quantities are being linked to the existence and progress of an abdominal aortic aneurysm (AAA), indicating that it might serve as an AAA biomarker. The efficacy of exosomes in anticipating and screening for maternal diseases has additionally been verified. Maternal circulation exosomal miRNAs, especially PDEs, are being shown to serve as important biomarkers for the prompt identification of gestational diabetes during pregnancy and premature delivery. The reduction in quantities of certain inhibitory synaptic molecules observed in plasma neuron-based exosomes has been suggested to function as a marker for mental loss, indicating the

development of Alzheimer's syndrome even 10 years before clinical presentation. Another team reported in 2019 recommended the development of Parkinson's disorder has been linked with changes in exosomal proteins that could potentially be used as biomarkers for evaluating the progression of the disease [13]. A further investigation indicated that exosomal miRNAs could serve as markers for schizophrenia and differentiate between the illness's different progression forms [14]. The miRNA and exosomal protein studies can also help predict and evaluate heart transplant rejection [15]. Burrello et al., established a combined kidney exosome evaluation technique that can identify the likelihood of transplanted kidney rejections by evaluating the exosome pattern obtained from individuals' urine samples [16]. Table **2** lists major clinical investigations that have identified biomarkers for prognosis as well as progression of the disease.

3.4. Monitoring the Treatment Response

Several plasma-based (exosomal) proteins along with RNA biomarkers (miR-222-3p, miR-21, exosomal SART1 peptide, PD-L1, miR-29a-3p, exo-RNAs, and exosomal EGFR) were discovered for the evaluation of response to treatment in various malignancies investigations, such as lymphoma, lung cancer, colorectal cancer, lung adenocarcinoma, melanoma, NSCLC, and esophageal cancer. Aside from being utilized in cancer therapeutic tracking, exosomes have been effective in assessing responses to treatment for various illnesses, such as cardiovascular as well as neurological conditions, and are more suitable for assessing graft rejection following transplantation of organs. A further investigation proposed that tiny extracellular vesicles might be employed to observe negative reactions in people receiving surgical cardiac valve replacement. Table **3** lists clinical scenarios and trials that used exosomes as possible biomarkers for evaluating response to treatment.

Table 3: Selective studies reported about the FBs tool-based exosomal biomarkers for NCDs treatment (clinical trials) and monitoring the response.

NCDs FB sample	Biomarkers	NCDs	Reference
Plasma	Exosomal SART1 peptide	Esophageal cancer	[54, 60]
Serum	Exosomes	Aortic valve replacement	[55]
Plasma	PD-L1	Melanoma	[56]
Plasma	miR-29a-3p	Colorectal cancer	[57]
Serum	miR-451	Lymphoma	[21]
Plasma	Exo-RNA	Lung cancer	[57]

3.5. Exosome-based FB Limitations

The sudden rise in the function of exosomes in therapeutic uses has brought focus to the establishment of fast and substantial volume methods to perform the biophysical as well as biological characterization of

exosomes [17]. The investigation of a biofluid-derived unique exosome that retains its biological function is difficult and necessitates more thorough research in this area. Some of the challenges that are preventing exosomal use in FBs are highlighted below.

3.6. Clinical Reproducibility

A further obstacle while using exosomes for FB is clinical confirmation and comparability with different biomarker systems. The diverse composition of exosomes, which originate from cells with varying traits, makes it challenging to validate their dosage and effectiveness [18]. As a result, sharing information between different studies as well as clinical trials becomes more difficult. The effectiveness and quantity of exosomes will be evaluated and standardized, making it easier to evaluate findings across examinations. Exosome immunity, stability, and safety must be assessed at every processing stage before they can be used in clinical trials [19].

3.7. Exosome-based FB-technical Advances

The increased use of exosomes in medical studies necessitates efforts to address all related constraints. Exosomal scientific investigation has made considerable progress in recent years, with the introduction of many extremely modern methods for exosome separation, analysis, and quantification [17]. The growing field of exosomes necessitates a computerized, quick, and accessible technique that is effective for future downstream uses. Furthermore, MISEV 2018 standards completely suggested I). to determine the quantitative indicators of origin material together with the measurement of extracellular vesicles (EVs); II). To characterize the EVs to provide assurance they contain plentiful EVs; III). To identify the existence of related elements [20], such as positive marker; and IV). To identify the existence of non-vesicle elements, that is, negative biomarker for every prior analysis. As a result, some new extraction techniques and mixtures of approaches were employed in current clinical trials to increase exosome production, pureness, and feasibility for downstream uses, including the Vn96-peptide-based approach, the anion-exchange technique, the exosome entire isolation chip, different microfluidic platforms, as well as the integration of sized exclusion chromatography as well as the process of ultrafiltration [21]. Upon isolating exosomes, description is an important step in determining their quantity and quality, particularly since they are to be employed in medical procedures including FBs and treatments. Exosome categorization ensures that the specific biomarker and treatment benefit corresponds to exosomes alone, rather than anything else like cell debris and other substances recovered with such exosomes [22].

3.8. The Marketing of Exosome-based Technologies and Commodities

Recently, exosome-based technology has seen a surge in commercial success. Acknowledging the possibilities of exosomes in diagnosing illnesses and treatments, an increasing variety of business entities have appeared and have begun to make investments in the creation and commercialization of exosome-based therapeutics [23]. They are biotechnological enterprises that create and market exosome-based approaches as well as goods. Exosomes employed in medical treatments are classified as medicines and biological materials in the Federal Food Drug and Cosmetic Act, and Public Health Service Act they need approval from the FDA in the 'Publicity Safety Notice' issued on December 6, 2019 [24]. In April 2018, the Aegle Therapeutics Corp became the initial company to obtain FDA permission to start clinical trials in patients with burns using an exosome-based product [25]. Several companies (Exosome Dx, IntelliScore, Avalon GloboCare Corp., Aegle Therapeutics Corp., Codiak Biosciences, and so on) are creating exosome-based diagnosing as well as treatment platforms for future use in clinical trials [26]. An ExoDx Prostate EPI testing serves as an exosome-based prostate cancer screening test created by exosome diagnostics, which is now owned by Bio-Techne [27]. Another biomarker-based diagnostic created through this company is an exosome-based screening for EGFR T790M in NSCLC instances, which minimizes redundant tumor biopsies while being accurate and precise than conventional cfDNA-based tumor biopsies. Codiak Biosciences produced ExoSTING™ as well as exoIL™, modified exosomes for medical treatment. Avalon GloboCare Corp., working together with GenExosome Techniques, additionally created diagnostic methods for identifying the saliva-related (miR-185) exosome miRNA biomarkers and to identify human angiogenesis exosomes.

4. Conclusions

FB has gained popularity as a noninvasive, rapid, and repeatable technique in medical settings, with an average yearly increase of approximately 19% between 2021 and 2032. Exosomes have shown promise as innovative biomarkers in FB, offering new avenues for early detection, prognosis, treatment monitoring, and NCD development. However, the application of exosome-based FB in medical facilities remains in its early stages and is not widely accepted for diagnosing various diseases, particularly cancer. Current methods for isolating and analyzing exosomes have limited sensitivity due to the variation between exosome subgroups. Moreover, collaborative efforts are needed to develop affordable techniques, with high levels of specificity, sensitivity, and purification for exosome identification and molecular content detection.

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Ethical Statement

The research is exclusively based on published literature; Ethical Approval is not required.

Conflict of Interest

The authors declare that there is no conflict of interest.

Artificial Intelligence (AI) Disclosure Statement

AI-unassisted work.

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Author Contribution

Mathiyazhagan Narayanan: Conceptualization, data analysis, writing, and reviewing the manuscript. Mani Ayyandurai: Writing and reviewing the manuscript. V. Rajinikanth: Writing and reviewing the manuscript.

Data Sharing Statement

All data generated during this report have been included in the article.

References

[1] Connal S, Cameron JM, Sala A, Brennan PM, Palmer DS, Palmer JD, et al. Liquid biopsies: The future of cancer early detection. J Transl Med. 2023 Feb;21(1):118.

[2] Di Bella MA. Overview and update on extracellular vesicles: Considerations on exosomes and their application in modern medicine. Biology (Basel). 2022 May;11(6):804.

[3] Ratajczak MZ, Ratajczak J. Extracellular microvesicles/exosomes: Discovery, disbelief, acceptance, and the future? Leukemia. 2020 Dec;34(12):3126–3135.

[4] Dwivedi M, Ghosh D, Saha A, Hasan S, Jindal D, Yadav H, et al. Biochemistry of exosomes and their theranostic potential in human diseases. Life Sci. 2023 Feb;315:121369.

[5] Yu W, Hurley J, Roberts D, Chakrabortty SK, Enderle D, Noerholm M, et al. Exosome-based liquid biopsies in cancer: Opportunities and challenges. Ann Oncol. 2021 Apr;32(4):466–477.

[6] Huda MN, Nafiujjaman M, Deaguero IG, Okonkwo J, Hill ML, Kim T, et al. Potential use of exosomes as diagnostic biomarkers and in targeted drug delivery: Progress in clinical and preclinical applications. ACS Biomater Sci Eng. 2021 Jun;7(6):2106–2149.

[7] Avgoulas DI, Tasioulis KS, Papi RM, Pantazaki AA. Therapeutic and diagnostic potential of exosomes as drug delivery systems in brain cancer. Pharmaceutics. 2023 May;15(5):1439.

[8] González Á, López-Borrego S, Sandúa A, Vales-Gomez M, Alegre E. Extracellular vesicles in cancer: challenges and opportunities for clinical laboratories. Crit Rev Clin Lab Sci. 2024 Sep;61(6):435–457.

[9] Barrachina MN, Calderón-Cruz B, Fernandez-Rocca L, García Á. Application of extracellular vesicles proteomics to cardiovascular disease: Guidelines, data analysis, and future perspectives. Proteomics. 2019 Jan;19(1-2):e1800247.

[10] Bejleri J, Jirström E, Donovan P, Williams DJ, Pfeiffer S. Diagnostic and prognostic circulating microRNA in acute stroke: A systematic and bioinformatic analysis of current evidence. J Stroke. 2021 May;23(2):162–182.

[11] Wu X, Xia P, Yang L, Lu C, Lu Z. The roles of long non-coding RNAs in Alzheimer's disease diagnosis, treatment, and their involvement in Alzheimer's disease immune responses. Noncoding RNA Res. 2024 Mar;9(3):659–666.

[12] Abdel-Haq H. The potential of liquid biopsy of the brain using blood extracellular vesicles: The first step toward effective neuroprotection against neurodegenerative diseases. Mol Diagn Ther. 2020 Dec;24(6):703–713.

[13] Vilaça-Faria H, Salgado AJ, Teixeira FG. Mesenchymal stem cells-derived exosomes: A new possible therapeutic strategy for Parkinson's disease? Cells. 2019 Feb;8(2):118.

[14] Raghavan V, Bhomia M, Torres I, Jain S, Wang KK. Hypothesis: Exosomal microRNAs as potential biomarkers for schizophrenia. Med Hypotheses. 2017 Jun;103:21–25.

[15] Khachatoorian Y, Khachadourian V, Chang E, Sernas ER, Reed EF, Deng M, et al. Noninvasive biomarkers for prediction and diagnosis of heart transplantation rejection. Transplant Rev (Orlando). 2021 Jan;35(1):100590.

[16] Burrello J, Monticone S, Burrello A, Bolis S, Cristalli CP, Comai G, et al. Identification of a serum and urine extracellular vesicle signature predicting renal outcome after kidney transplant. Nephrol Dial Transplant. 2023 Feb;38(3):764–777.

[17] Boriachek K, Islam MN, Möller A, Salomon C, Nguyen NT, Hossain MS, et al. Biological functions and current advances in isolation and detection strategies for exosome nanovesicles. Small. 2018 Feb;14(6):1702153.

[18] Mehryab F, Rabbani S, Shahhosseini S, Shekari F, Fatahi Y, Baharvand H, et al. Exosomes as a next-generation drug delivery system: An update on drug loading approaches, characterization, and clinical application challenges. Acta Biomater. 2020 Sep;113:42–62.

[19] Rezaie J, Feghhi M, Etemadi T. A review on exosomes application in clinical trials: Perspective, questions, and challenges. Cell Commun Signal. 2022 Sep;20(1):145.

[20] Welsh JA, Goberdhan DC, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, et al.; MISEV Consortium. Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches. J Extracell Vesicles. 2024 Feb;13(2):e12404.

[21] Yadav R, Singh AV, Kushwaha S, Chauhan DS. Emerging role of exosomes as a liquid biopsy tool for diagnosis, prognosis, monitoring treatment response of communicable & non-communicable diseases. Indian J Med Res. 2024 Feb;159(2):163–180.

[22] Marjani AA, Nader ND, Aghanejad A. Exosomes as targeted diagnostic biomarkers: recent studies and trends. Life Sci. 2024 Oct;354:122985.

[23] Jafari D, Shajari S, Jafari R, Mardi N, Gomari H, Ganji F, et al. Designer exosomes: A new platform for biotechnology therapeutics. BioDrugs. 2020 Oct;34(5):567–586.

[24] Wang CK, Tsai TH, Lee CH. Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci. 2024 Aug;17(8):e13904.

[25] Davies OG, Williams S, Goldie K. The therapeutic and commercial landscape of stem cell vesicles in regenerative dermatology. J Control Release. 2023 Jan;353:1096–1106.

[26] Castellanos-Rizaldos E, Grimm DG, Tadigotla V, Hurley J, Healy J, Neal PL, et al. Exosome-based detection of EGFR T790M in plasma from non–small cell lung cancer patients. Clin Cancer Res. 2018 Jun;24(12):2944–2950.

[27] Li L, Zhang L, Montgomery KC, Jiang L, Lyon CJ, Hu TY. Advanced technologies for molecular diagnosis of cancer: State of pre-clinical tumor-derived exosome liquid biopsies. Mater Today Bio. 2022 Dec;18:100538.

[28] Fotuhi SN, Khalaj-Kondori M, Hoseinpour Feizi MA, Talebi M. Long non-coding RNA BACE1-AS may serve as an Alzheimer's disease blood-based biomarker. J Mol Neurosci. 2019 Nov;69(3):351–359.

[29] Elbay A, Ercan Ç, Akbaş F, Bulut H, Ozdemir H. Three new circulating microRNAs may be associated with wet age-related macular degeneration. Scand J Clin Lab Invest. 2019 Oct;79(6):388–394.

[30] Hannafon BN, Trigoso YD, Calloway CL, Zhao YD, Lum DH, Welm AL, et al. Plasma exosome microRNAs are indicative of breast cancer. Breast Cancer Res. 2016 Sep;18(1):90.

[31] Armstrong DA, Green BB, Seigne JD, Schned AR, Marsit CJ. MicroRNA molecular profiling from matched tumor and bio-fluids in bladder cancer. Mol Cancer. 2015 Nov;14(1):194.

[32] Dong L, Lin W, Qi P, Xu MD, Wu X, Ni S, et al. Circulating long RNAs in serum extracellular vesicles: Their characterization and potential application as biomarkers for diagnosis of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1158–1166.

[33] Arbelaiz A, Azkargorta M, Krawczyk M, Santos-Laso A, Lapitz A, Perugorria MJ, et al. Serum extracellular vesicles contain protein biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. Hepatology. 2017 Oct;66(4):1125–1143.

[34] Zubiri I, Posada-Ayala M, Sanz-Maroto A, Calvo E, Martin-Lorenzo M, Gonzalez-Calero L, et al. Diabetic nephropathy induces changes in the proteome of human urinary exosomes as revealed by label-free comparative analysis. J Proteomics. 2014 Jan;96:92–102.

[35] Biró O, Alasztics B, Molvarec A, Joó J, Nagy B, Rigó J Jr. Various levels of circulating exosomal total-miRNA and miR-210 hypoxamiR in different forms of pregnancy hypertension. Pregnancy Hypertens. 2017 Oct;10:207–212.

[36] Zhang H, Huang E, Kahwaji J, Nast CC, Li P, Mirocha J, et al. Plasma exosomes from HLA-sensitized kidney transplant recipients contain mRNA transcripts which predict development of antibody-mediated rejection. Transplantation. 2017 Oct;101(10):2419–2428.

[37] Perez-Hernandez J, Olivares D, Forner MJ, Ortega A, Solaz E, Martinez F, et al. Urinary exosome miR-146a is a potential marker of albuminuria in essential hypertension. J Transl Med. 2018 Aug;16(1):228.

[38] Cheow ES, Cheng WC, Lee CN, de Kleijn D, Sorokin V, Sze SK. Plasma-derived extracellular vesicles contain predictive biomarkers and potential therapeutic targets for myocardial ischemic (MI) injury. Mol Cell Proteomics. 2016 Aug;15(8):2628–2640.

[39] Salomon C, Guanzon D, Scholz-Romero K, Longo S, Correa P, Illanes SE, et al. Placental exosomes as early biomarker of preeclampsia: Potential role of exosomal microRNAs across gestation. J Clin Endocrinol Metab. 2017 Sep;102(9):3182–94.

[40] Sukma Dewi I, Celik S, Karlsson A, Hollander Z, Lam K, McManus JW, et al. Exosomal miR-142-3p is increased during cardiac allograft rejection and augments vascular permeability through down-regulation of endothelial RAB11FIP2 expression. Cardiovasc Res. 2017 Apr;113(5):440–452.

[41] McKiernan J, Donovan MJ, O'Neill V, Bentink S, Noerholm M, Belzer S, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncol. 2016 Jul;2(7):882–889.

[42] Goetzl EJ, Abner EL, Jicha GA, Kapogiannis D, Schwartz JB. Declining levels of functionally specialized synaptic proteins in plasma neuronal exosomes with progression of Alzheimer's disease. FASEB J. 2018 Feb;32(2):888–893.

[43] Rodríguez-Martínez A, de Miguel-Pérez D, Ortega FG, García-Puche JL, Robles-Fernández I, Exposito J, et al. Exosomal miRNA profile as complementary tool in the diagnostic and prediction of treatment response in localized breast cancer under neoadjuvant chemotherapy. Breast Cancer Res. 2019 Feb;21(1):21.

[44] Lin Y, Dong H, Deng W, Lin W, Li K, Xiong X, et al. Evaluation of salivary exosomal chimeric GOLM1-NAA35 RNA as a potential biomarker in esophageal carcinoma. Clin Cancer Res. 2019 May;25(10):3035–3045.

[45] Fernandez-García CE, Burillo E, Lindholt JS, Martinez-Lopez D, Pilely K, Mazzeo C, et al. Association of ficolin-3 with abdominal aortic aneurysm presence and progression. J Thromb Haemost. 2017 Mar;15(3):575–585.

[46] Kennel PJ, Saha A, Maldonado DA, Givens R, Brunjes DL, Castillero E, et al. Serum exosomal protein profiling for the non-invasive detection of cardiac allograft rejection. J Heart Lung Transplant. 2018 Mar;37(3):409–417.

[47] Jiang R, Rong C, Ke R, Meng S, Yan X, Ke H, et al. Differential proteomic analysis of serum exosomes reveals alterations in progression of Parkinson disease. Medicine (Baltimore). 2019 Oct;98(41):e17478.

[48] Salomon C, Scholz-Romero K, Sarker S, Sweeney E, Kobayashi M, Correa P, et al. Gestational diabetes mellitus is associated with changes in the concentration and bioactivity of placenta-derived exosomes in maternal circulation across gestation. Diabetes. 2016 Mar;65(3):598–609.

[49] Ebrahimkhani S, Vafaee F, Young PE, Hur SS, Hawke S, Devenney E, et al. Exosomal microRNA signatures in multiple sclerosis reflect disease status. Sci Rep. 2017 Oct;7(1):14293.

[50] Li L, Li W, Chen N, Zhao H, Xu G, Zhao Y, et al. FLI1 exonic circular RNAs as a novel oncogenic driver to promote tumor metastasis in small cell lung cancer. Clin Cancer Res. 2019 Feb;25(4):1302–1317.

[51] Alegre E, Sanmamed MF, Rodriguez C, Carranza O, Martín-Algarra S, González A. Study of circulating microRNA-125b levels in serum exosomes in advanced melanoma. Arch Pathol Lab Med. 2014 Jun;138(6):828–832.

[52] Lea J, Sharma R, Yang F, Zhu H, Ward ES, Schroit AJ. Detection of phosphatidylserine-positive exosomes as a diagnostic marker for ovarian malignancies: A proof of concept study. Oncotarget. 2017 Feb;8(9):14395–14407.

[53] Bijnsdorp IV, Geldof AA, Lavaei M, Piersma SR, van Moorselaar RJ, Jimenez CR. Exosomal ITGA3 interferes with non-cancerous prostate cell functions and is increased in urine exosomes of metastatic prostate cancer patients. J Extracell Vesicles. 2013 Dec;2(1):22097.

[54] Liang C, Zhang L, Lian X, Zhu T, Zhang Y, Gu N. Circulating exosomal SOCS2-AS1 acts as a novel biomarker in predicting the diagnosis of coronary artery disease. BioMed Res Int. 2020 Apr;2020:9182091.

[55] Weber A, Liu SS, Cardone L, Rellecke P, Sixt SU, Lichtenberg A, et al. The course of circulating small extracellular vesicles in patients undergoing surgical aortic valve replacement. BioMed Res Int. 2020 Apr;2020:6381396.

[56] Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature. 2018 Aug;560(7718):382–386.

[57] Parakrama R, Fogel E, Chandy C, Augustine T, Coffey M, Tesfa L, et al. Immune characterization of metastatic colorectal cancer patients post reovirus administration. BMC Cancer. 2020 Jun;20(1):569.

[58] Manna S, Tripathy S, Sah RK, Padhi BK, Kaur S, Nowrouzi-Kia B, et al. The burden of non-communicable diseases (NCDs) among prisoners in India: A systematic review and meta-analysis. Healthcare (Basel). 2022 Oct;10(10):2046.

[59] Padhi BK, Singh S, Gaidhane AM, Abu Serhan H, Khatib MN, Zahiruddin QS, et al. Inequalities in cardiovascular disease among elderly Indians: A gender perspective analysis using LASI wave-I (2017-18). Curr Probl Cardiol. 2024 Jul;49(7):102605.

[60] Nalinipriya G, Suneetha M, Mikhailova M, Ramesh SN, Kumar KV. Leveraging double-valued neutrosophic set for real-time chronic kidney disease detection and classification. Int J Neutrosophic Sci. 2025 Jan;(1):279–290.