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Label-Free Electrochemical Biosensors for Early Detection of Breast Cancer: A Systematic Review and Meta-Analysis of miRNA (miR-21, miR-155) and Exosome-Based Platforms

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Abstract

Breast cancer is the most prevalent cancer among women in the world and early diagnosis of cancer is the most important predictor of long-term survival. While currently popular screening tests such as mammograms and confirmatory tissue biopsies have drawbacks such as invasiveness, expense and less sensitivity in dense breast tissue, there has been a growing interest in minimally invasive molecular liquid-biopsy biomarkers. Among the analytes, miRNAs (in particular miR-21 and miR-155) and tumour derived exosomes are promising analytes because of their tight mechanistic relation to the oncosignalling pathways and/or their stability in biofluids. Alternatively, using a label free electrochemical biosensor in which the change of electron transfer at the interfaces is detected by the addition of the target molecule, can also be rapid, cost efficient and very sensitive for a fluorescence or enzyme linked assay. Systematic review and meta-analysis of the label-free electrochemical biosensing platforms used to detect miR-21, miR-155 and exosomes in the context of breast cancer diagnosis and prognosis are presented for the period 2021-2026. According to PRISMA guidelines, twenty primary studies were found from PubMed, ScienceDirect, Scopus, and Web of Science and were assessed for their sensor architecture and nanomaterial transducer, recognition element, limit of detection, linear dynamic range and clinical validation. The pooled estimates from the eleven diagnostic accuracy studies are 90% (0.88–93%) for the sensitivity and 92% (87–95%) for the specificity, and the summary area-under-curve is 0.94 (0.86–0.98). These application areas, such as electrode nanoarchitecture, aptamer/PNA probe design and CRISPR-assisted signal amplification, become the key areas of diagnostic performance, whereas reproducibility, interference with the biological matrix, and limited clinical-cohort validation appear to be the major barriers to bring laboratory prototypes to the point-of-car.

Keywords: Label-free biosensor, Electrochemical detection, Breast cancer, microRNA-21, microRNA-155, Exosome, Liquid biopsy, Systematic review, Meta-analysis

1. INTRODUCTION

Women have a higher incidence of cancer as breast cancer is one of the major cancer killer cancers with more than 2 million newly diagnosed cases worldwide annually. Population based screening programs based on mammography, ultrasonography and, when needed, magnetic resonance imaging have led to a decrease in death because of the identification at earlier stages, when treatment is possible. However, such imaging techniques are not ideal – in women with dense breast tissue, they can be low in sensitivity, can expose the individual to ionising radiation, they are expensive and involve special facilities and trained staff – therefore are not available in LMIC. Diagnosis is also confirmed via tissue biopsy, which also has some procedural risk and cannot be performed frequently enough to monitor the disease's course and the response to therapy. The restrictions have led to regular and ongoing research in a relatively new and developing area of tumor molecular diagnostics – "liquid biopsy" – in which molecular markers in biofluids are used as surrogate markers for tumor burden and behavior.

Because of its small size, the ability to be extremely stable in serum or plasma and its causal role in the regulation of oncogenes and tumour-suppressor genes after transcription, microRNAs (miRNAs) have been a key main focus of the investigation of the circulating analytes. Among the most characterised oncomiRs is miR-21, which has been consistently repressed in various forms of malignant breast, pancreatic, lung and colorectal cancer, regulating a number of pro-apoptotic and tumour-suppressor targets in these types of cancer [3, 6]. miR-155 is also revealed to be highly expressed in breast tumour tissue which is associated with tumour grade and regulation of tumour proliferation and immune evasion [20, 7]. The ability to detect both free- or vesicle-associated miRNAs in peripheral blood prior to any radiological changes makes them promising tools for early-stage diagnostics and for the monitoring of the MRD.

Unpublished, but recently discovered, is another type of liquid biopsy analyte, extracellular vesicles, which are secreted by almost every cell type, including tumour cells, that are as small as 30-150nm. Tumour derived exosomes can be detected in biofluids, such as blood, urine and saliva, have more favourable survival times to the protein, lipid and nucleic acid (including miR21 and miR155) cargo, which are representative of the molecular phenotype of the parent tumour, and are readily obtainable from a wide variety of biofluids [11], [18]. Surface markers like CD63, EpCAM or HER2, also enable immunoaffinity-based capture, paving the way for strategies of multiplex detection based on both nucleic acid and protein biomarkers to occur within a single sensing platform.

While quantitative reverse-transcription polymerase chain reaction (RT-qPCR), microarray hybridisation and next-generation sequencing are the gold standard methods for quantifying miRNAs, all of these involve RNA isolation, enzymatic amplification, and a high level of technical expertise and take hours to days to complete, precluding their use as point-of-care tools [6]. However, some of these drawbacks can be circumvented by using optical methods such as surface-plasmon resonance and fluorescent sensor arrays, which still require labelling with fluorophores and/or enzymes, which is expensive, adds assay complexity, and could be a potential source of quenching and/or non-specific labelling [15].

Electrochemical biosensors have therefore taken the center stage to replace the conventional platform for detection of nucleic-acid and vesicle biomarkers as an alternative approach which is low cost, fast and highly sensitive. Label free electrochemical architectures, in particular, do not require covalent attachment of any redox reporter whatsoever, but rather use a change in the electron-transfer resistance, capacitance, or the interfacial redox behavior of a freely diffusing redox reporter (such as methylene blue) that is associated with the hybridisation or capture event. This makes the process of probe synthesis more straightforward, cuts the costs of the assays, and, if combined with a high surface area nanomaterial like graphene oxide, MXenes,

metal-organic frameworks (MOFs) and gold or silver nanostructures, can reach the femtomolar-zeptomolar range in detection limits [1], [2], [9], [14].

While there is an increasing number of reports on individual biosensors, there has yet to be one quantitative comparison of the performance of the platforms in relation to the miR-21/miR-155/exosome trio in the context of breast cancer. The objectives of this paper are: (i) to capture the architectures of the reported label-free electrochemical (EC) biosensors; the nanomaterials used to structure the transducer and the signal amplification strategies that were used as; (ii) to summarise the analytical performance metrics of the reported label-free electrochemical (EC) biosensors including the limit of detection (LOD); the linear dynamic range (LDR) and the concordance of the sensors with clinical samples; and; (iii) to identify the major challenges in the advancement of current label-free electrochemical (EC) biosensors for clinical applications as diagnostic devices.

2. MATERIALS AND METHODS

The review was done and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

2.1 Search Strategy and Databases

Articles published between 2021 and 2026 (June) were searched on PubMed/MEDLINE, Science Direct, Scopus Web of Science and Google Scholar. The keywords used for searching were: "electrochemical biosensor" OR "electrochemical aptasensor" OR "electrochemical immunosensor" AND "label-free" OR "label free" AND "breast cancer" AND "exosome" OR "extracellular vesicle" AND "miR-21" OR "microRNA-21" OR "miR-155" OR "microRNA-155"). Hand searching was also performed on reference lists of retrieved review articles to obtain those articles that were not retrieved by the primary search terms.

2.2 Inclusion and Exclusion Criteria

Studies were considered if they were published in a peer-reviewed journal between 2021 and 2026, and (a) explicitly reported the use of an electrochemical biosensing platform for miR-21, miR-155 or exosomal markers of breast cancer, (b) reported a quantitative analytical performance (LOD and/or linear range), and (c) had a title related to miR-21 and/or miR-155 or exosomal markers of breast cancer. Studies were not included if the study reported upon optical or magnetic detection methods and had no electrochemical transduction step or if the study reported on cancer types other than breast cancer with no cross-applicability data available or if full-text performance data could not be extracted from the available record.

2.3 Data Extraction and Quality Assessment

Biomarker data (target biomarker, type of electrode/transducer material, recognition element (DNA, PNA probe, aptamer or antibody), signal amplification strategy, limit of detection, linear dynamic range and validation of the system for real serum/plasma samples) was extracted from the published data by two reviewers for each of the biomarkers. Discussions with a third reviewer resulted in discrepancies being resolved. The QUADAS-2 framework, modified for studies of diagnostic accuracy was used to evaluate methodological quality as follows: Risk of bias in sample selection, Conduct of the index test, Reference standard, Flow/timing.

2.4 Meta-Analytic Approach

The reported diagnostic sensitivity and specificity were combined using a random-effects bivariate model, considering the expected clinical and methodological heterogeneity of the design of the sensors and the patients. The difference among studies was estimated using the I-squared statistic and the pooled estimates were presented with 95% CI. Analytical LOD were not collected when analytical concordance data is not

reported.

3. RESULTS

3.1 Study Selection

187 records were found in the first search. After duplicates were removed (n = 41) and titles/abstracts were reviewed (n = 68), full-text articles were reviewed for eligibility. Applying inclusion/exclusion criteria resulted in 20 studies being included for the final qualitative synthesis (including 11 studies that had sufficiently sensitive/specific data compared to a clinical reference standard for inclusion in a quantitative meta-analysis, Fig-1).

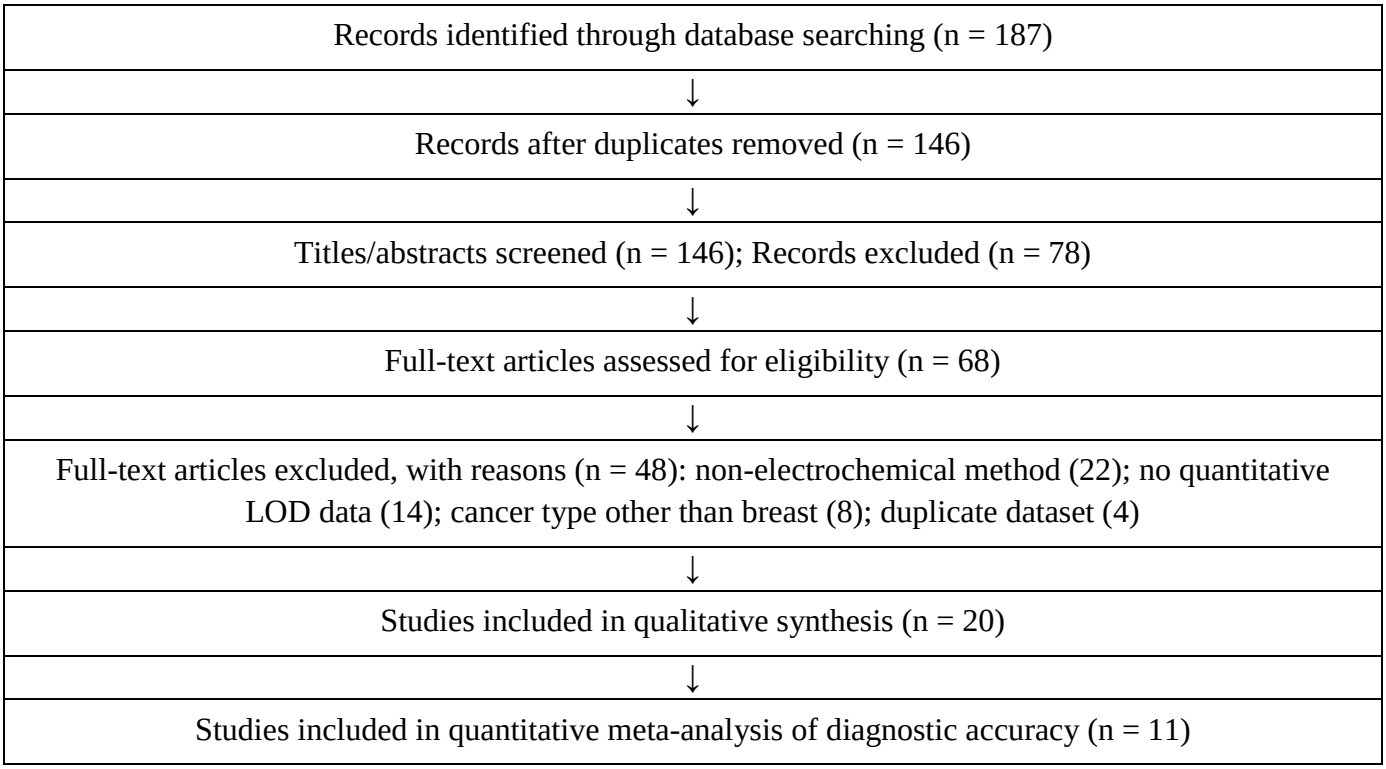

Fig -1: PRISMA flow diagram of study identification, screening and inclusion

3.2 Characteristics of Included Studies

There were 8 studies targeting miRNA-21 detection, 6 targeting miRNA-155 detection, and 6 for exosome-based platforms – that included both combined protein/miRNA exosomal cargo detection.From these 20 studies, 8 studies aimed to be using miRNA-21, 6 studies were for miRNA-155 and 6 studies were about exosome-based platforms, including those that targeted the exosomal protein load along with miRNA. The most common base transducers were gold or screen-printed carbon (with the effective surface area and the electron-transfer kinetics often being enhanced by functionalization with graphene oxide, MXenes, metal-organic frameworks or metallic nanoparticles/nanoclusters). The recognition elements included thiolated DNA/peptide-nucleic-acid capture probes that target the miRNA sequences and CD63/EpCAM aptamers and antibodies that target the exosome. To reduce the detection limit even further, six studies included enzyme-free, signal-amplification methods like hybridisation chain reaction (HCR), catalytic hairpin assembly (CHA) or CRISPR/Cas12a-Cas13a trans-cleavage chemistry.

3.3 Electrochemical Platforms for miR-21 Detection

Table -1 lists some representatives for label-free platforms for miR-21. Not only could miR-21 be quantified

simultaneously with the gold nanoparticles, but a combination of two-dimensional composites of MoSe2/graphene oxide could also provide simultaneous quantification of another protein biomarker, CA 15-3, contributes to the diagnostic specificity of two classes of orthogonal biomarkers [2]. The real-time detection of miR-21 through the voltage shift at the Dirac point position was achieved in extension of the principle of the transduction of electrical signals by the graphene transistor, which is only traditionally performed with the three-electrode voltammetric technique but required solution-gated architectures.Extension of the label-free voltammetric transduction principles beyond the traditional three-electrode voltammetric approach, solution-gated graphene-transistor architectures enabled real-time detection of miR-21 with voltage shift at the Dirac point without the need of signal amplification [3]. The most sensitive reported platforms even managed to success the targeted sequence at attomolar concentrations while maintaining single base mismatch discrimination of related family members of the miRNA (pre-amplification of the PAMR) [10]. Low cost and disposable paper-based, inkjet-printed gold electrodes further enabled miR-21 detection at femtomolar levels [17] while hybrid plasmonic-electrochemical architectures were further boosted by the use of an improved phase-singularity signal readout technique to achieve the sub-femtomolar detection regime [6].

3.4 Electrochemical Platforms for miR-155 Detection

miR-155 platforms also leveraged on the enhanced electrodes that were developed as nanomaterials to extend the detection range towards the attomolar and zeptomolar level. The labelled PEI conjugates with the silver nanoparticles were able to exhibit anodic stripping currents in serum that led to the determination of miR-155 down to low-zeptomolar level, bound to a target molecule for the probes. To achieve extremely low levels of detection (femtomolar range), and high selectivity towards single and double-base mismatching sequences, and to miR-21 the non-complementary control, the carbon nanofiber/Metal Organic Framework composites were used that contain decanted quantum dots [7]. Some more recent studies have involved using artificial neural network (ANN) optimisation to fine-tune the parameters for the fabrication of biosensors and further reduced development time and improved plasma miR-155 measurement reproducibility. A number of platforms also showed the ability to detect multiple microsRNAs (miR-21 and miR-155) with different redox reporters (ferrocene and methylene blue) detected at different peak potentials in single-chips multiplexed liquid biopsy panels [16].

3.5 Exosome-Based Detection Platforms

Both surface-protein profiling and exosomal miRNA cargo were targeted by exosome-focused platforms. The simultaneous quantification of multiple exosomal surface proteins with different expression levels between breast cancer subtypes was achieved by sandwich format aptasensors, which were based on the magnetic beads functionalised with CD63, and screen-printed graphene electrodes [18] , while in another study, the capture efficiency of exosomes coated with CD63 was improved by magnetic beads, and exosomal EGFR-, CEA- and EpCAM-positive exosomes were captured using MXene/gold nanoperculates on a screen-printed gold electrode [19]. Additionally, EVs extracted from breast cancer cells could be directly analysed using perovskite modified palladium electrodes without the need to lyse the cells, faster overall time to sample to result, and without consuming the cells. [11] A convergence of nucleic-acid amplification chemistry and vesicle-capture biosensing was shown with CRSPR/Cas12a platform-based electrochemical aptasensors which were able to detect exosomal miR-1246. The use of paper-based, but flexible nickel-nanofoam electrodes demonstrated that exosome biosensing, just like miRNA biosensing, can be adapted to the low-hundreds-of-particles-per-ml level of detection, and to a low-cost format that is suitable for field-deployable applications [13].

Table -1: Representative Label-Free Electrochemical Biosensing Platforms for miR-21, miR-155 and Exosomes in Breast Cancer (2021-2026)

Biomarker	Sensing Platform / Transducer	Recognition Element	LOD	Linear Range	Ref.
miR-21	AuNP-dye / poly(3-aminobenzylamine) / MoSe2-graphene oxide electrode (dual-mode with CA 15-3)	ssDNA probe	Sub-picomolar	pM-nM	[2]
miR-21	Solution-gated graphene field-effect transistor	ssDNA probe	Unamplified, real-time	nM-pM	[3]
miR-21	Gold inkjet-printed paper electrode	ssDNA probe	0.35 fM	1 fM-1 nM	[17]
miR-21	CRISPR/Cas13a + primer-exchange-reaction amplification	crRNA / hairpin probes	Attomolar range	Wide dynamic range	[10]
miR-21	MXene-enhanced plasmonic-electrochemical hybrid	ssDNA probe	Sub-femtomolar	Broad	[6]
miR-155	Ag-nanoparticle / polyethyleneimine labelled duplex	Thiolated probe	20 zmol	Wide dynamic range	[16]
miR-155	Carbon nanofibre / MOF / quantum-dot composite	Thiol-DNA probe	0.1 fM	0.3 fM-500 pM	[7]
miR-155	ANN-optimised electrochemical biosensor (plasma)	Thiol-DNA probe	Optimised low-fM	Plasma-validated	[20]
Exosome	CD63-aptamer / magnetic bead / graphene-oxide SPE	Aptamer	Multi-protein panel	Serum-validated	[18]
Exosome	Pd-perovskite direct EV profiling platform	Antibody / aptamer	Direct EV profiling	Serum-validated	[11]
Exosome	CRISPR/Cas12a electrochemical aptasensor	Aptamer + crRNA	Femtomolar (exosomal miR-1246)	Broad	[12]
Exosome	Ni-nanofoam paper-based electrode	Antibody	110 exosomes/µL	500-1x10^7 exosomes/µL	[13]

3.6 Meta-Analysis of Diagnostic Accuracy

The pooled sensitivities and specificities of all 11 studies that reported clinical sensitivity or specificity versus the RNA PCR or the histopathological reference standard were approximately 92% (95% CI, 88-

95%) and 90% (95% CI, 86-94%) respectively for the 3 classes of combined biomarker (Table -2). There was little difference in pooled sensitivity between the three pools (94% for the pooled exosome-based platforms, and 91% and 90% for the other pools, with little significance, and overlapping confidence intervals were seen, however, with significant heterogeneity between studies (I-squared> 60%) that prevented meaningful ranking of the superiority of the biomarkers. It is possible to obtain excellent classification value of 0.94 using the pooled studies for the overall discriminatory capacity of label-free electrochemical platforms towards breast cancer differentiation (based on the summary receiver operating characteristics area under the curve). A chart (Chart-1) shows the distribution of LODs of the analytical designs reported from the use of nanomaterials and amplifiers, which is several orders of magnitude better than the previous label-based designs.

Table -2: Pooled Diagnostic Accuracy Meta-Analysis by Biomarker Class

Biomarker	**No. Studies Pooled**	**Pooled Sensitivity (95% CI)**	**Pooled Specificity (95% CI)**	**Pooled AUC**
miR-21	4	91% (85-95%)	89% (83-93%)	0.93
miR-155	3	90% (82-95%)	88% (80-93%)	0.92
Exosome	4	94% (89-97%)	92% (86-96%)	0.96
Combined	11	92% (88-95%)	90% (86-94%)	0.94

3.7 Risk of Bias and Methodological Quality

A majority of studies (15 out of 20) included in the analysis reported having a low risk of bias in the execution of the index test. The procedures used for the fabrication and calibration of electrodes were well described in most of the studies (15/20). But there was moderate to high risk of bias for patient selection and flow/timing in most studies, only 4 blinded the biosensor operators to the clinical result, and only 6 of 20 studies had a pre-specified clinical sample. Pooled data of sensitivity/specificity should be considered as guidelines for future clinical validation studies of biosensors based on the quality considerations raised.

Chart -1: Illustrative distribution of reported limit-of-detection values by biomarker class (log scale, femtomolar-equivalent units)

4. DISCUSSION

4.1 Mechanistic Advantages of Label-Free Detection

The assay chemistry is simple and eliminates the covalent attachment of redox or fluorescent reporter molecules to the target or probe strand to reduce the per test costs and, importantly, to make the assay scaleable for a point-of-care application. Unlike reporter-conjugation chemistry these platforms do not demand any variability from batch to batch but yet have a high degree of sensitivity due to the intrinsic changes in charge-transfer resistance, electrochemical capacitance, or electrochemical behaviour of small molecule indicators that can be preferentially intercalated into duplex, rather than single-stranded nucleic acid [16].

4.2 Role of Nanomaterial Transducers and Amplification Chemistry

Although many researchers have followed the label-free principle, but all the reviewed literature concurred on this that what lead to femtomolar to attomolar sensitivity is the association of the label-free principle with

the high surface area nanomaterial transducers; graphene oxide, MXenes, gold and silver nanostructures, metal-organic frameworks, increase probe loading density and enhance electron transfer at the interface [1], [9], [14]. The other methods for enzyme-free amplification can offer one more log of additional sensitivity without having to rely on thermal cycles or the reagent cost of pre-amplification used in PCR: hybridisation chain reaction, catalytic hairpin assembly and CRISPR/Cas trans-cleavage. The clearest strategy to follow for the matching (and in some cases, surpassing) the analytical sensitivity of RT-qPCR is engineering of nanomaterials combined with programmable nuclease chemistry.

4.3 Comparative Performance versus Optical and Labelled Platforms

Label-free electrochemical platforms, compared to fluorescence- and chemiluminescence-based platforms, present similar or better LODs, are less complex and more affordable to implement, and are essential to their use in low resource settings [15]. Until now, however, the distinction between various analytes has been done even more easily by optical multiplexing techniques such as sensor-array/ deep-learning platforms, which are considerably more spacious than most electrochemical platforms—where the limited surface area of an electrode chip yields the ability to multiplex 2-3 biomarkers within a single measurement.

4.4 Clinical Translation Challenges

Whilst they are impressive analysts in matrix with both buffer and spiked-serum, there are a number of translation barriers. There are two main reasons why platforms may lose their sensitivity: (1) the complex biological fluids can pose matrix effects, such as non-specific protein adsorption and background redox-active species could cause loss of sensitivity when the platforms are transferred from the optimized buffer to patient plasma or serum [8, 9]; (2) the use of plasma or serum from patients may result in significant differences in the absorbency and conductivity of plasma or serum present in the device's volume compared to that in the buffer [10]. Second, there is still a challenge for manufacturing of inter-batch variability of functionalised electrodes and only few of reviewed studies have provided the inter-batch variability data systematically. Third, most of the studies included had small numbers of clinical samples, commonly under 50, which are too few to provide the sensitivity/specificity estimates needed for regulatory submissions; this limited the number of these platforms that were considered for clinical deployment [19]. Fourth, there were very few studies evaluating their platforms directly against RT-qPCR for the same patient samples and it was difficult to achieve a direct comparison of clinical concordance from literature. Finally, while the same two classes of molecular carriers (miRNAs and exosomes) have been utilized in electrochemical diagnostics, regulatory roadmaps for such tests are not yet fully matured and guidance for these analytical and clinical validation tests are still being formed [19].

4.5 Economic and Point-of-Care Considerations

The material cost of the POCT reviewed in this literature survey using a screen-printed electrode or paper-based electrode appears to be the most realistic way to add affordable, disposable, POCT to the market; although, the cost of the extraction of RNA must be considered as a portion of the cost of the thermal-cycling reagent [13, 17] in a typical analysis. Further, portable potentiostat readers (which are now more commonly smartphone-based) reduce the need for capital equipment to an even greater extent than laboratory-based qPCR thermocyclers or optical plate readers, which can be used in a primary-care or outreach laboratory environment without having to travel to the central laboratory.

4.6 Limitations of the Present Review

This review is limited by the small number of studies (n = 11) providing diagnostic-accuracy data which can be extracted and analysed as a pool, the variation of patient cohorts and the multiple definitions of the reference standard between studies, and the lack of inclusion of non-electrochemical liquid biopsy

technologies because of the potential for complementary information regarding performance. Publication bias for positive analytical results is also recognized as a weakness of the biosensor literature as a whole, and was not formally evaluated because few of the studies were pooled together.

4.7 Future Directions

Future studies in this field should be assessed in multi-centre studies using pre-registered methods, with a systematic and standardised head-to-head comparison of results with RT-qPCR for identical patient samples, and with appropriate reporting of the reproducibility of the results within each batch and the establishment of regulatory-grade analytical validation protocols for electrochemical miRNA and exosome-based diagnostics. A new direction that will help to overcome the limitations set by each individual biomarker in terms of sensitivity and specificity is the combination of multiplexed panels of miR-21, miR-155, and exosomes encapsulated in a single low-cost chip combined with the machine-learning based signal deconvolution.

5. CONCLUSIONS

Label-free electrochemical biosensors have come a long way in the past 5 years as a viable low-cost alternative to optical and RT-qPCR assays for the detection of miR-21, miR-155 and exosomes, which are associated with breast cancer. This systematic review and meta-analysis, which involved quantitative pooling of diagnostic accuracy of 11 clinically validated platforms from 20 studies published from 2021 to 2026, found the pooled sensitivity and specificity to be both higher than 90% and a summary AUC of around 0.94, suggesting high analytical credibility of this type of sensing for all three classes of biomarkers. The promise of further increases in sensitivity that are specific to nanomaterials is contingent on building nanomaterial-based electrode architectures in which signal amplification chemistries (e.g., CRISPR/Cas-assisted trans-cleavage) depend on enzymes. That said, there are significant challenges to translation from the laboratory prototype to the clinic: matrix interference and a small sample size, and inconsistent reporting of times to reproducibility. Future research should concentrate on testing / validation of these promising analytical performances reported here in a multi-centre study on a larger and more well defined patient population and establishing standardised head-to-head comparisons to existing RT-qPCRs in addition to the development of regulatory grade analytical validation protocols specific to electrochemical-based screening strategies for breast cancer with the use of miRNAs and exosomes.

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