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REVIEW ARTICLE

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Identification of diagnostic biomarkers used in the diagnosis of cardiovascular diseases and diabetes mellitus: A systematic review of quantitative studies

Megan Wilson BSc[1] | Abdullah Al-Hamid PhD[2] | Ismail Abbas PhD[3] | Jason Birkett PhD[1] | Iftikhar Khan PhD[1] | Matthew Harper PhD[4] | Dhiya Al-Jumeily OBE PhD[4] | Sulaf Assi PhD[1]

[1]Faculty of Science, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK

[2]Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, AlAhsa, Saudi Arabia

[3]Faculty of Science, Lebanese University, Beirut

[4]Faculty of Engineering and Technology, School of Computer Science and Mathematics, Liverpool John Moores University, Liverpool, UK

Correspondence
Megan Wilson, Faculty of Science, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, L3 5AH, UK.
Email: m.wilson3@2019.ljmu.ac.uk

Abstract

Aims: To perform a systematic review of studies that sought to identify diagnostic biomarkers for the diagnosis of cardiovascular diseases (CVDs) and diabetes mellitus (DM), which could be used in low- and middle-income countries (LMICs) where there is a lack of diagnostic equipment, treatments and training.

Materials and Methods: Papers were sourced from six databases: the British Nursing Index, Google Scholar, PubMed, Sage, Science Direct and Scopus. Articles published between January 2002 and January 2023 were systematically reviewed by three reviewers and appropriate search terms and inclusion/exclusion criteria were applied.

Results: A total of 18 studies were yielded, as well as 234 diagnostic biomarkers (74 for CVD and 160 for DM). Primary biomarkers for the diagnosis of CVDs included growth differentiation factor 15 and neurogenic locus notch homologue protein 1 (Notch1). For the diagnosis of DM, alpha-2-macroglobulin, C-peptides, isoleucine, glucose, tyrosine, linoleic acid and valine were frequently reported across the included studies. Advanced analytical techniques, such as liquid chromatography mass spectrometry, enzyme-linked immunosorbent assays and vibrational spectroscopy, were also repeatedly reported in the included studies and were utilized in combination with traditional and alternative matrices such as fingernails, hair and saliva.

Conclusions: While advanced analytical techniques are expensive, laboratories in LMICs should carry out a cost–benefit analysis of their use. Alternatively, laboratories may want to explore emerging techniques such as infrared, Fourier transform-infrared and near-infrared spectroscopy, which allow sensitive noninvasive analysis.

KEYWORDS
diabetes complications, heart failure, meta-analysis, type 2 diabetes, type 1 diabetes, cardiovascular disease

1 | INTRODUCTION

The ever-growing prevalence of cardiovascular diseases (CVDs) and diabetes mellitus (DM) is made apparent by the World Health's Organization, which states that 17.9 million and 1.5 million lives are lost annually to CVDs and DM, respectively.[1,2] In fact, 80% of people with CVDs/DM are from low- and middle-income countries (LMICs) including Bangladesh, India and some African nations.[3-5] The prevalence of the aforementioned diseases can be attributed to epidemiological transitions and rapid urbanization, which have caused negative changes to the public's diet and lifestyle behaviours.[6] Consequently, the CVD and DM epidemic has created a significant burden on already strained healthcare systems in LMICs. This results in a limited number of resources, treatments and therapies for CVD and/or DM management. Therefore, many patients are likely to develop additional life-threatening complications such as diabetic nephropathy, heart failure and myocardial infarction.[7-11]

The limited funding and resources available in LMICs provides an explanation for the misuse of advanced analytical techniques, such as electrocardiogram (ECG). For the diagnosis of CVDs, ECG interpretation requires advanced user knowledge, a lack of which can create misdiagnosis, mistreatment and further complications. The lack of sufficient equipment also explains the misdiagnosis of DM through the electrochemical method, which was identified in a previous systematic review.[12] While the electrochemical method of glycated haemoglobin (HbA1c) and fasting plasma glucose measurement is deemed the 'gold standard' for DM diagnosis, it is frequently unfeasible for LMICs, where there is a lack of adequate equipment and facilities.[3-5] Hence, it is imperative that cheaper diagnostic approaches are explored. Through the identification of such methods, the number of diagnostic errors is likely to be reduced and disease management/treatment greatly improved. Therefore, the aim of this systematic review was to identify a range of diagnostic techniques and CVD and DM biomarkers.

2 | MATERIALS AND METHODS

2.1 | Study design

A systematic literature search was conducted to identify diagnostic biomarkers and techniques used for the diagnosis of CVDs and DM. The study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Data S1).[13]

2.2 | Search strategy

For study collection, six databases were selected: the British Nursing Index, Google Scholar, PubMed, Sage, Science Direct and Scopus. The results were filtered to include articles published between January 2002 and January 2023. A set of search terms was applied to all databases, which included key words such as 'analysis', 'biomarkers', 'cardiovascular disease', 'detection', 'diabetes mellitus', 'identification', 'detection' and 'metabolites'. Article titles were first evaluated by two reviewers (M.W. and S.A.) in terms of relevance and, if deemed eligible, underwent full review by a third reviewer (I.A.). The systematic review protocol was registered at PROSPERO (CRD42023483319).[14]

2.3 | Selection criteria

Studies that looked at the identification of biomarkers used in the diagnosis of CVDs and DM were included. To ensure that disease diagnosis occurred during the early prognosis stage, participants in the eligible studies were adults (aged 18–65 years old). Reviews, meta-analyses and editorials were excluded. Studies that looked at diagnosis through genes or microbes were excluded as outside the study's scope.

2.4 | Study selection and data extraction

M.W. and S.A. first screened the titles and abstracts of all retrieved papers. One of three options was selected by the reviewers, those being: include, exclude or unsure. In cases where a disagreement was encountered, or a reviewer could not make a conclusive decision, discussion was carried out with all reviewers. The first and third reviewers (M.W. and I.A.) reviewed the full papers and M.W. collated information from accepted studies related to study design, study setting, population age, sample size, biological matrix and biomarkers (Table 1).

2.5 | Assessment of study quality

The quality of the included studies was determined via the Critical Appraisal Skills Programme, which also determined the relevance of included systematic reviews.[15] An additional tool, the Newcastle-Ottawa Scale quality tool, was employed to judge the quality of case–control and cohort studies.[16]

TABLE 1 Information extracted from included papers.

Sections	Subsections
Title	Aim of study
Study characteristics	Experimental settings, sample size, study design, population and instrumentation
Extraction procedure	Cleaning procedures, sample type/size, storage and storage conditions
Experimental conditions	Diagnostic technique used and parameters
Biomarkers	Type of biomarker, concentration and regulation

2.6 | Data analysis

The median and interquartile range (IQR) were calculated using SPSS and Microsoft Excel. Quantitative data were pooled in a statistical meta-analysis where possible. In cases where high heterogeneity was suspected, findings are shown as a narrative summary; hence, figures and tables have been used to improve presentation.

3 | RESULTS

3.1 | Study extraction

A total of 3 640 260 articles were screened through the selected databases, of which 2764 were assessed in the initial reviewing process (Figure 1). Based on the relevance of titles and application of the inclusion/exclusion criteria, 2574 papers were excluded. The abstracts of the remaining 190 studies were reviewed and 37 excluded. After full-text review, 18 studies were deemed eligible and underwent quality reassurance through quality tools. Each study received a star rating of one to three, three being the highest and one the lowest. Studies with three stars were eligible and included within the review. If a study scored two stars, it was included but reviewed with caution, while studies that scored one or no stars were not eligible for inclusion. After the application of quality assessment tools, 17 studies received a three-star rating[17-27,29-34] and one study a two-star rating.[28] Thus, a total of 18 studies were accepted and included in the review.

3.2 | Study characteristics

The characteristics of the included studies are shown in Appendix 2.1. Articles were filtered between 2002 to 2023, with the earliest included article published in 2008. The included studies' sample size ranged from 23 to 7184, with a median range of 117 (IQR 75–640). With regard to study design, 12 studies were case–control studies,[17,18,20,21,23-27,30,31,33] two were cohort studies,[32,34] three were prospective case–control studies[19,28,29] and one was a prospective cohort study.[22] The aforementioned studies used patients recruited from 12 countries, including: Belgium,[18] Brazil,[26] China,[17,20,22,30,34] India,[23,28] Iraq,[19] Mexico,[33] Netherlands,[29] Pakistan,[31] Spain,[32] Sweden,[24,25] Turkey[27] and the United States.[21] The study settings included hospitals ($n = 7$) and laboratories ($n = 11$). When reported,

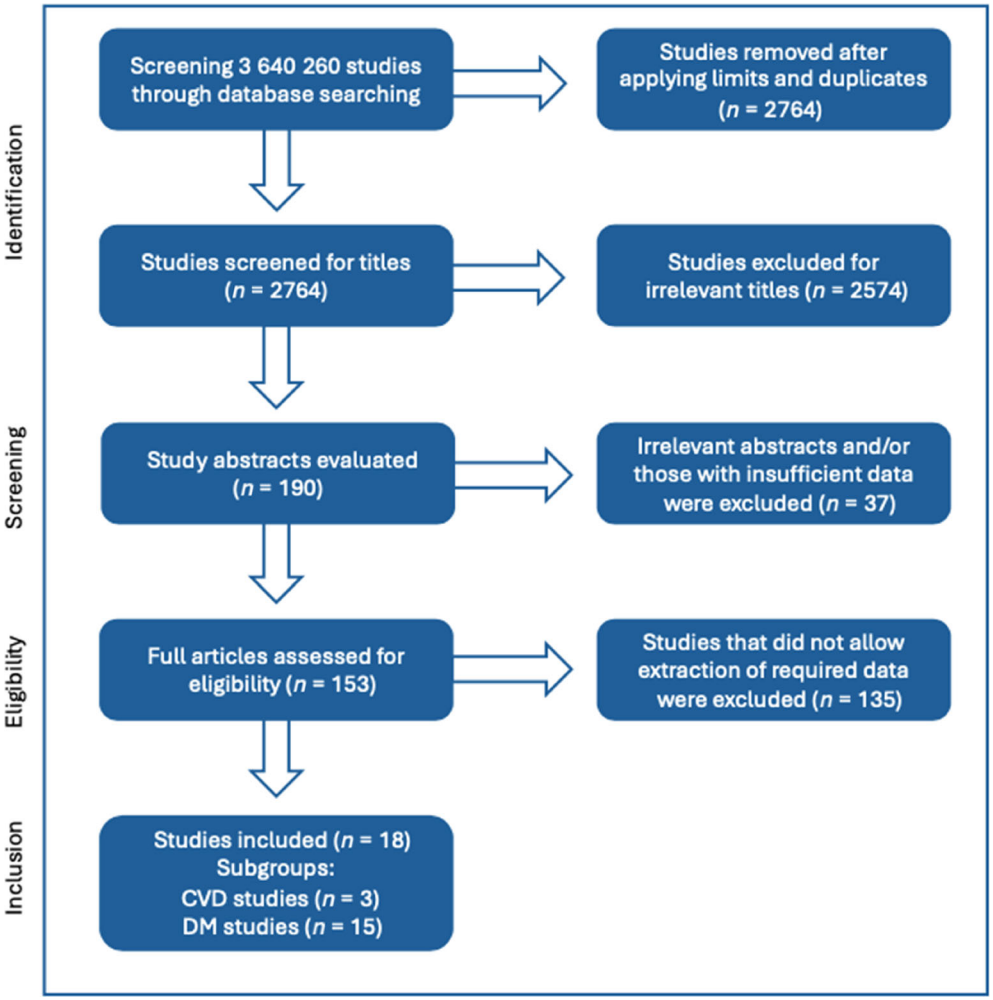

FIGURE 1 Data extraction process and study selection workflow.

TABLE 2 Characteristics of participants in the included studies.

Study number	Age range, years	Male: Female	Population size	Non-disease: disease
1[17]	30–61	67:80 (46:54)	147	53:94 (36:64)
2[18]	28–34	80:79 (51:49)	159	107:52 (67:59)
3[19]	18–34	44:39 (53:47)	83	42:41 (51:49)
4[20]	40–60	84:0 (100:0)	84	42:42 (50:50)
5[21]	30–60	366:274 (57:43)	640	523:117 (82:18)
6[22]	35–63	3289:3895 (46:54)	7184	6737:447 (94:6)
7[23]	30–60	241:188 (56:44)	429	216:213 (50.3:49.7)
8[24]	45–65	1017:1244 (45:55)	2261	1911:350 (85:15)
9[25]	42–58	443:563 (44:56)	1006	503:503 (50:50)
10[26]	18–65	NR	23	2:21 (8:92)
11[27]	30–61	24:38 (39:61)	62	23:39 (37:63)
12[28]	36–62	NR	40	20:20 (50:50)
13[29]	45–65	74:0 (100:0)	86	12:74 (14:86)
14[30]	48–61	81:68 (54:46)	149	48:101 (32:68)
15[31]	20–55	NR	41	20:21 (49:51)
16[32]	24–43	29:46 (39:61)	75	25:50 (33:67)
17[33]	30–50	69:12 (85:15)	81	32:49 (40:60)
18[34]	40–59	NR	767	0:100 (0:100)

the duration of studies was between 2 months and 5 years with a median of 2 years and 6 months (IQR 11 months–3 years and 3 months).

3.3 | Participant characteristics

Details regarding the participants' characteristics, including age, non-disease: disease ratio, male: female ratio and population size, are shown in Table 2. As previously mentioned, the studies included participants aged between 18 and 65 years (median [IQR] 45 [35–53] years). Where reported, the median male: female ratio for participant ages in case–control, cohort and prospective case–control studies were 241:188 (IQR 73.5:404.5–79.5:418.5), 75:29 (IQR 59:9–81.75:51.5) and 59:19.5 (IQR 51.9:9.75–66.5:29.25) years, respectively.

3.4 | Identified biomarkers

Seven biological matrices were used for the diagnosis of CVD and/or DM. These included blood,[17] fingernails,[18,19] hair,[18] plasma,[20-25,29] saliva,[26-28] serum[30,31,33] and urine.[32,34] Plasma and urine were employed in the diagnosis of CVDs, whereas blood, fingernails, hair, plasma, saliva and serum were used for the diagnosis of DM.

In addition, 234 biomarkers (74 CVD and 160 DM biomarkers) were reported for the diagnosis of CVDs and DM (Appendices 2.2 and 2.3). Of the 234 biomarkers, four were used in both CVD and DM participants: alanine, collagen, cystatin-C and leptin.[17,18,21,22,25,26,28-30,33,34] It is worth noting that most of the reported biomarkers were highlighted once across the 18 included studies, and this infrequent identification of the highlighted biomarkers could explain the lack of quantifiable reference and diagnostic ranges.

3.4.1 | CVD biomarkers

A total of 74 CVD biomarkers were identified (Appendix 2.2). Growth differentiation factor 15 (GDF15) was identified in two of the included studies, where it was detected in plasma[22] and urine.[32] In plasma, GDF15 was observed within the range of 1200–1800 pg/mL and was specifically related to the diagnosis of atherosclerosis, atrial fibrillation, coronary artery disease and hypertension.[61,62] Similarly, levels of GDF15 were elevated in urine from the healthy range of 537–931 pg/mL to 1044–2555 pg/mL in CVD patients.[100] GDF15 is a stress-induced transforming growth factor-β superfamily cytokine and has previously been associated with stress and inflammation that causes tissue damage. Elevated levels of GDF15 can provide an indication of disease progression and prognosis and may act as a therapeutic target in future work. Neurogenic locus notch homologue protein 1 (Notch1) was also detected in both plasma[22] and urine.[32] Despite two studies observing Notch1, no quantification of this biomarker occurred.

3.4.2 | DM biomarkers

For the diagnosis of DM, 163 biomarkers were extracted (Appendix 2.3). Several biomarkers, including alpha-2-macroglobulin (A2M), C-peptides, isoleucine, glucose, tyrosine, linoleic acid and

valine, were reported two or more times across the included studies.[19-21,23,25,29,30] Isoleucine was detected in plasma and reported in three studies.[20,21,25] Previously, this biomarker has been observed at elevated levels of 107 ± 32.3 and 143.4 ± 23.6 μmol/L in type 1 (T1DM) and type 2 DM (T2DM) cases, respectively.[123] Similarly, C-peptides offered the advantage of specific diagnostic ranges for T1DM and T2DM and were detected in fingernails ($n = 1$), hair ($n = 1$) and plasma ($n = 1$).[19,21] In fingernails and hair, C-peptides were seen at levels of ~20–45 pg/mg in T1DM cases and ~ 40–145 pg/mg in healthy controls.[19] In plasma, C-peptide levels between 0.3–0.6 nmol/L were deemed as healthy, while downregulated C-peptide levels (<0.03 nmol/L) were specific to T1DM and upregulated levels (>2.0 nmol/L) were characteristic of T2DM.[112,113] C-peptides also offer therapeutic potential for treatment of diabetic complications, particularly in T1DM.[113]

It is important to note the overlap between health reference and diagnostic ranges for biomarkers within the literature. For example, previous work revealed an overlap between healthy (792.19 ± 116.59 μg/mL) and diabetic (845.43 ± 101.10 μg/mL) levels of complement factor B for the diagnosis of T2DM.[31] The overlap between healthy reference and diagnostic ranges may create diagnostic error. Thus, laboratories should look at employing several biomarkers during the diagnosis process to maximize diagnostic potential. Alternatively, laboratories may also choose to employ gold standard biomarkers such as glucose, which offers defined diagnostic ranges and detectability in several biological matrices including blood,[17] plasma[21] and saliva.[28] While blood and saliva provided an indication of DM, glucose detected in plasma was identified at specific levels for T1DM (176.7 ± 82.5 mg/dL) and T2DM (154.1 ± 33.8 mg/dL).[123] The high levels of glucose seen in both T1DM and T2DM are highly specific due to abnormalities seen in insulin production. As a result, glucose is left unmetabolized and builds up in the bloodstream.[18] If left untreated, people with DM are likely to develop hyperglycaemia and further diabetic complications such as diabetic ketoacidosis.

3.5 | Methods of Identification

The techniques employed for the identification of CVD and DM biomarkers varied across the published data. Techniques reported included: ECGs,[29] enzyme-linked immunosorbent assay (ELISA),[21,22,28,32] Fourier-transform infrared spectroscopy (FT-IR),[26] gas chromatography (GC)-flame ionization detector,[23] GC–mass spectrometry (MS),[20,21] infrared (IR) spectroscopy,[27] liquid chromatography (LC)-MS[24,25] LC–tandem MS (LC–MS/MS),[21] nano-LC–MS/MS,[31] near-infrared (NIR) spectroscopy,[17,18] proton magnetic resonance spectroscopy,[29] proton nuclear magnetic resonance spectroscopy,[34] target MS,[32] ultra-high performance liquid chromatography-Q Exactive hybrid quadrupole-orbitrap high-resolution accurate MS,[30] ultrafast GC (e-Nose),[33] (Appendix 2.4).

Five studies used LC–MS methods for the identification of CVD and DM biomarkers in plasma ($n = 3$),[21,24,25] saliva ($n = 1$)[28] and serum ($n = 1$).[31] To validate a metabolic panel for the early diagnosis of T2DM, LC–MS/MS was applied.[21] The application of this technique revealed increased levels of branched-chain amino acids (isoleucine, leucine and valine), tyrosine, mannose and 2-hydroxybutyrate and decreased levels of glycine, lysophosphatidylcholine C18:2 and 1,5-anhydrosorbitol in DM. Untargeted LC–MS was also applied to identify plasma biomarkers.[25] A comparison was made using 187 case–control pairs and identified 46 predictive plasma biomarkers including phosphatidylcholines and 2-hydroxyethanesulphonate.[25]

The use of ELISAs for the detection of CVD and DM biomarkers in plasma ($n = 2$) and urine ($n = 1$) was also reported.[21,22,32] Through the application of a multiplex ELISA, a metabolic panel for the early detection of T2DM was validated.[21] This technique also demonstrated significant differences between concentrations of diagnostic proteins including eosinophil cationic protein, GDF15 and guanine deaminase in cases versus healthy controls.[32] Furthermore, the relationship between biological sex and diagnostic biomarker concentration was identified through a modified ELISA approach.[22] A total of 71 biomarkers were detected, 61 (86%) of which displayed significant differences in male and female participants. From the 61 biomarkers, 37 were higher in females, with leptin, ceruloplasmin and hemopexin showing the largest differences between males and females.[22]

Four studies utilized vibrational spectroscopic techniques including FT-IR ($n = 1$), IR ($n = 1$) and NIR ($n = 2$) spectroscopy for the detection of diagnostic biomarkers in blood ($n = 1$),[17] fingernails ($n = 1$)[18] and saliva ($n = 2$).[26,27] FT-IR spectra suggested that differences between controls and diabetic participants were present in the fingerprint region between 600 and 1300 cm^{-1}. Research also focussed on bands at 1076 cm^{-1} (vibrational mode of skeletal cis conformation of DNA), 1403 cm^{-1} (symmetric CH3 bending modes of protein methyl groups and bending CH_3 of collagen) and 1451 cm^{-1} (asymmetric CH3 bending of protein methyl groups).[26] Scott et al.[27] identified strong bands at 2852 and 2926 cm^{-1}, which originated from symmetric and asymmetric stretching of lipid acyl CH_2 groups, respectively. Furthermore, NIR spectroscopy was applied to fingernails and focused on the region, 4150–6150 cm^{-1} for the detection of DM biomarkers.[18] For example, band 4666 cm^{-1}, attributed to $CONH_2$ stretching band, increased in broadness when glycation increased.[18]

4 | DISCUSSION

The findings of this review suggest the capabilities of a range of diagnostic biomarkers for the diagnosis of CVDs and DM. The studies included in the review frequently reported the detection of GDF15 and Notch1 for the diagnosis of CVDs, and of A2M, C-peptides, isoleucine, linoleic acid, tyrosine and valine for the diagnosis of DM. However, it is worth noting that the lack of a quantified reference range for several of the detected biomarkers suggests that further research within the field of diagnostic biomarker detection and quantification is required. Moreover, this may imply that laboratories are more likely to employ gold standard biomarkers that have set diagnostic ranges such as glucose.

While previous systematic reviews focused on the use of traditional biological matrices (blood, plasma and serum), this review collated a number of biomarkers from traditional and alternative matrices including fingernails, hair and saliva.[18,19,26] The noninvasive nature and simple sampling procedure of alternative matrices are appealing to patients, therefore, are likely to improve compliance rates for diagnostic monitoring and reduce diagnostic errors. Hence, these matrices are highly beneficial for LMICs, where sampling equipment is limited.[3-5] Other reviews focused on a single biological matrix and subsequently limited the number of diagnostic biomarkers identified.[143,144] This review adds to the previous literature and provides important insights for laboratories, healthcare institutions and researchers working with CVDs and DM.

In relation to the concentration of biomarkers, laboratories should consider confounding variables such as biological sex. Previous research made apparent the relationship between biological sex and CVD biomarker concentration.[145] For example, female subjects were found to have a higher concentration of C-reactive protein in comparison to male subjects (2.56 vs. 1.43 mg/L).[146] A previous review also made evident the differences in concentrations of adiponectin and leptin between females and males, with females often showing higher levels.[51] Sex-specific variation can be attributed to differences seen in risk factors and behavioural habits such as high blood pressure, cholesterol, smoking and obesity. This explains why CVDs are often perceived as a 'man's disease' and misdiagnosed in females.[147]

It is worth mentioning that several of the recorded techniques employed in LMICs for the detection of biomarkers are expensive. Nevertheless, their repeated use in both developed and developing countries can be attributed to their high level of accuracy, precision and sensitivity. Therefore, LMICs are likely to invest in expensive techniques to improve diagnostic capabilities/results. Nevertheless, the high costs of techniques mean that the number of laboratories equipped with advanced instrumentation is limited. For example, techniques such as LC–MS/MS may only be offered at private hospitals in the most affluent areas. However, laboratories should carry out cost–benefit analyses and determine the overall benefits of using advanced techniques that offer high levels of accuracy, precision, sensitivity and selectivity for biomarker detection. The employment of such techniques is likely to reduce the number of diagnostic errors and improve patients' treatment/management. In this regard, LC–MS/MS is a highly desirable technique for the diagnosis of CVDs and DM. The addition of tandem MS/MS allows for high sensitivity and the detection of a wide range of biomarkers.[148] LC–MS/MS also offers the advantages of accuracy and specificity, which are key for the prevention of diagnostic errors[148] Likewise, ELISAs are frequently employed for diagnosis based on their ability to sensitively detect a wide range of target analytes.[64] The addition of an ELISA sandwich approach guarantees further sensitivity required for diagnostic biomarker detection. However, in cases of diagnostic biomarkers sharing similar structures, cross-reactivity may occur and cause false-positive or false-negative readouts.[149]

Vibrational spectroscopic techniques such as IR, FT-IR and NIR spectroscopy offer cost-effective, nonintrusive and noninvasive biomarker detection. In comparison to gold standard techniques for CVD and DM diagnosis, which include cardiac catheterization and the electrochemical method, vibrational spectroscopy offers the advantage of working with noninvasive and nonintrusive biological matrices including fingernails and hair. The application of such matrices, reduces sample preparation costs and instrumentation maintenance and improves patient compliance rates. The ability of IR and FT-IR spectroscopy to identify chemical structures is highly beneficial for disease detection. Furthermore, NIR offers additional information regarding a sample's physiochemical structure, hence it can be used in combination as a complementary technique. Unlike the gold standard techniques, which often target one or two biomarkers during analysis, vibrational spectroscopy allows the detection of a wide range of biomarkers.[150] Furthermore, despite the low sensitivity and specificity of many diagnostic biomarkers, vibrational techniques have worked in combination with a range of biological matrices including bile,[151] bladder wash,[152] blood, fingernails, saliva, sputum[153,154] and urine for the diagnosis of bladder cancer, CVDs, DM, oral cancer, oropharyngeal cancer, ovarian cancer and laryngeal cancer.[18,26,27,29]

4.1 | Implications for practice

Many LMICs do not have the facilities, staff and/or expenses to frequently administer diagnostic tools and collect matrices, therefore, several patients develop further disease-related complications. However, through the application of alternative matrices and nontraditional analytical techniques, laboratories can reduce costs and frequencies of diagnostic errors, and improve patients' treatment/experience. Not only will this improve the patient's overall experience, which will in turn improve compliance rates and hospital visit attendance, but it will also improve the overall quality, accuracy and precision of laboratory findings. Moreover, through the analysis of alternative matrices, for example, fingernails, which can be collected in the patient's home and require minimal-to-no sample preparation, funding, previously utilized for diagnostic purposes, can be redistributed to disease management and treatment.

4.2 | Strengths and weaknesses

The studies accepted in this review identified a significant number of diagnostic biomarkers that can be employed by laboratories for the diagnosis of CVDs and DM. Furthermore, some studies included novel diagnostic techniques including vibrational spectroscopy, which offers rapid, noninvasive analysis of a range of biological matrices and biomarkers. Despite the rigorous and systematic reviewing process, limitations have still been encountered. Studies were variable in terms of design, technique and inclusion criteria. Hence, comparative conclusions between the published data are limited. For instance, studies utilized a range of analytical techniques to assess similar clinical outcomes. However, the lack of a standardized technique/approach for the identification of diagnostic biomarkers creates heterogeneity within the results. The variability with regards to sample size (23–7184, median 117, IQR 75–640) further contributed to heterogeneity

among the studies. Additionally, studies with smaller sample sizes (<40) were less likely to see statistically significant outcomes. It is also worth noting that the diagnostic criteria for CVDs and DM in the reviewed papers may vary. Based on the inconsistency of diagnostic criteria, findings could not be generalized.

5 | CONCLUSIONS

This review identifies emerging biomarkers for the diagnosis of CVDs and DM including GDF15, Notch1, isoleucine, tyrosine and valine. Moreover, this review complements previous systematic reviews by highlighting the use of traditional and alternative biological matrices, the latter of which offers noninvasive, nonintrusive sampling for improved diagnostic monitoring compliance rates. To improve disease diagnosis, laboratories should consider carrying out cost–benefit analysis of emerging advanced techniques. Despite their high costs, advanced techniques offer accurate and highly sensitive biomarker detection, which has the potential to reduce the number of diagnostic errors and the misadministration of treatment. Therefore, whilst initial costs may be high, emerging techniques such as LC–MS/MS and ELISA offer cost-effective diagnosis in the long term. The literature also revealed vibrational spectroscopic techniques, that offer cost-effective diagnosis with high sensitivity and selectivity. As an emerging technique, vibrational spectroscopy offers non-invasive, non-intrusive analysis that requires little-to-no sample preparation; thus, it is extremely cost-effective for LMICs. Future work will look at carrying out cost-effective analysis of the highlighted emerging techniques, as well as targeting frequently reported biomarkers in alternative matrices to determine their diagnostic efficacy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Megan Wilson https://orcid.org/0000-0002-9840-2272

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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