Review

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Novel putative biomarkers for infective endocarditis by serum proteomic analysis: a comprehensive review of literature

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Abstract

Infective endocarditis (IE) is a challenging condition with high mortality. Prompt detection of IE has become essential for early and immediate management. The authors aimed to comprehensively review the existing literature on novel putative biomarkers for IE through serum proteomic analysis. The literature reveals high levels of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels in IE with staphylococcal etiology, valvular lesions, and when combined with cardiac troponin I (cTnI), had a more significant value for risk stratification. A higher pro-ADM level, copeptin, NT-proBNP, and the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) all impacted mortality during the hospital stay. The biomarker matrix metalloproteinase-9 was utilized to predict new-onset embolic events in patients, thus serving as a predictive marker. Procalcitonin was an important diagnostic marker in IE complicated with severe infection. Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interferon-γ, cTnI, and NT-proBNP were also discovered to be useful as prognostic indicators. Early diagnosis and appropriate treatment are possible using antiphospholipid antibodies as a diagnostic test for definite IE. It is also concluded that antineutrophilic cytoplasmic antibody positive individuals with IE had a lengthier hospital stay. These noninvasive biomarkers can identify patients at risk and provide appropriate and early clinical management. NT-proBNP, Cystatin C, troponins, IL-6, IL-8, S100A11, and AQP9 are examples of possible markers that appear promising for further research. In conclusion, large-scale validation studies should study these biomarkers further to establish their use in clinical settings.

Keywords: infective endocarditis, infective heart disease, novel putative biomarkers, NT-proBNP, serum proteomic analysis

Introduction

Infectious endocarditis (IE) is a fatal infection affecting mainly heart valves through its pathological vegetative growth on the valves. The vegetation causes destructive effects on the tissue, increasing the risk of embolization, abscesses, and fistulas[1]. The discovery of accurate biomarkers for clinical use will improve early diagnosis and prognosis. The study proposes proteomic analysis to comprehend the dynamics of organisms, and mass spectrometry is an essential tool for protein profiling in cells[2]. Proteomic analysis is the systematic recognition and

HIGHLIGHTS

- Proteomic analysis studies have identified potential biomarkers for infective endocarditis (IE), including NT-proBNP, Cys C, troponins, S100A11, LBP, VCAM-1, AQP9, CD62E, and Interleukin-6 (IL-6).
- Commonly used biomarkers for IE have limited specificity, highlighting the need for more accurate diagnostic biomarkers.
- Specific biomarkers have been found for bacterial infections causing IE, such as ST 17 for Group B *streptococcus*, extracellular vesicle proteome for *Granulicatella adiacens*, and sortase family proteins for *Streptococcus mutans*.
- Multidisciplinary teams oversee IE management, including antibiotic therapy and potential surgery. Prognostic indicators like pro-ADM, copeptin, MHR, IL-17A, IL-10, sE-selectin, antineutrophil cytoplasmic antibody, procalcitonin, and NT-proBNP aid in risk stratification and treatment decisions.

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measurement of all the proteins present in a biological system at a given time[2].

The pathogenesis of IE, the host response, the infecting bacteria, and the identification of potential biomarkers have all benefited from studying vegetation proteomes. The protein composition of several species' IE vegetations may be comparable, with observed variations reflecting pathogen-specific reactions and unique clinical circumstances[1].

Initial studies found that commonly used biomarkers such as erythrocyte sedimentation rate, procalcitonin, C-reactive protein (CRP), rheumatoid factor, and NT-proBNP had limited specificity for diagnosing IE[3]. However, recent clinical proteomic profiling studies identified potential future biomarkers for IE, including NT-proBNP, Cys C, troponins, S100A11, LBP, VCAM-1, AQP9, CD62E, and Interleukin-6 (IL-6)[4]. Various proteomic analysis methods like LFQ LC-MS/MS, immunomeTM protein array system, and SELDI-TOF MS have been used to address the challenges of low specificity[5,6].

Osteoprotegerin levels were significantly expressed in the IE cohort per the 2D page technique. According to the immunome protein array system, interleukin-1 alpha (IL1A), tudor and KH domain-containing protein (TDRKH), nucleolar protein 4 (NOL4), G antigen 2B/2C (GAGE2) were among the proteins whose expression was significantly different between IE and non-IE controls[3]. While a serum signature with a protein index of seven proteins and a strong diagnostic profile for IE was assessed using the SELDI-TOF MS method[6]. For IE, pathogen-specific biomarkers have also been found, such as ST 17 by SELDI for Group B *streptococcus* (GBS) infection[7], the extracellular vesicle proteome for *Granulicatella adiacens*[8], and sortase family proteins for *Streptococcus mutans* infection[9]. The objective of the study is to show how several pathogen-specific biomarkers can be exploited in IE for clinical usage as diagnostic and monitoring tools[9].

Epidemiology

Over the past few years, several clinically and statistically significant changes have been noted in the epidemiological profile of IE[10]. Studies from the United States and Europe revealed that patients over the age of 50 accounted for 50% or more of IE cases[11,12]. For a long time, it was believed that the epidemiology of IE in nations with low or middle incomes was comparable to that of high-income nations in the, at the dawn of the antibiotic era[13]. However, we are observing that there is a trend shift towards low- and middle-income countries[13].

Oral *streptococci*, also known as *Viridans streptococci*, now come after *staphylococci* as the major etiology of IE, according to a meta-analysis of almost 26 publications written between 1993 and 2003 and a total of 3784 incidents of IE[10].

Congenital heart disorders and rheumatic heart disease are still the most important etiologies of IE in the Middle East[14].

Etiology and pathogenesis

IE is mainly caused by gram-positive bacterial organisms such as *Streptococcus*, *Staphylococcus*, and *Enterococcus*, with *S. aureus* being the most frequently associated. Another significant cause of this condition is the skin commensal *S. epidermidis*, which resides on indwelling catheters and is the primary cause of prosthetic valvular endocarditis. *Streptococci* (most commonly *S. viridans*), which are found in the oral, gastrointestinal, and genitourinary tract, are the primary etiological factor of IE in developing countries. In individuals with underlying colon cancer, group D *streptococci* such as *S. bovis* and *gallolyticus* are the cause of IE, where the bloodstream serves as a channel of spread[15].

In some cases, bacteria that are difficult to culture or have become noncultivable due to antibiotic use can contribute to culture-negative IE. Examples of such bacteria include *Coxiella burnetii*, *Bartonella* spp., and *Tropheryma*. Additionally, certain fungi like *Candida* and *Aspergillus* can cause rare cases of IE[16].

Pathogenic bacteria can enter the bloodstream through various routes and then attach to the valve surface. The damage to the valvular endothelium, often caused by turbulent blood flow, can make the valve surface more vulnerable to colonization by bacteria circulating in the blood. The release of inflammatory markers such as fibronectin, interleukins, and vascular adhesion molecules can facilitate the adherence of circulating platelets, fibrin, and polysaccharides with bacteria to the valve surface[15,17]. This complex, known as a vegetation, is a characteristic feature of IE and can be observed macroscopically[18].

Vegetation on the valve surface contributes to valvular damage and leads to a range of complications, including valve insufficiency, abscess formation, conduction abnormalities, bacteremia, and septic embolism to other organs such as the lungs, kidneys, brain, and skin[17].

Clinical features

The clinical history of IE varies greatly depending on the etiological microbe, whether pre-existing cardiac disease is present or not, and the method of presentation. It can sometimes manifest as an acute infection that progresses suddenly, but it can also be a subacute or chronic disease with diffuse symptoms that can obstruct or cloud the initial diagnosis[19].

IE manifests itself clinically as follows[20]:

1. Fever, which is generally around 100°F (38.4°C) and is associated with chills, rigors, anorexia, weight loss, and night sweats.
2. A new regurgitant murmur may fade as the condition worsens.
3. Skin lesions such as Osler's nodes, which are painful and present on thenar/hypothenar eminences and finger pulps.
4. Janeway lesions are painless macules and papules on the palms and soles.
5. Petechiae and splinter hemorrhages.
6. Roth spots (hemorrhages with pale centers and boat-shaped).
7. Splenomegaly, renal infarction, or glomerulonephritis.
8. Neurological symptoms such as cerebral emboli resulting in hemiplegia and sensory impairment, as well as mycotic aneurysms.

Up to 90% of patients appear with fevers, night sweats, exhaustion, and loss of appetite, and up to 25% have embolic symptoms at that time[21].

Diagnosis

Three criteria form the basis for the diagnosis of IE:

(1) Microbiological diagnosis.
(2) Echocardiography and other imaging modalities.
(3) Clinical criteria.

Table 1

Studies on putative biomarkers for infective endocarditis.

References	Date of publication	Study design	Method	Biomarkers identified	Conclusions
Zampino, *et al.*[36]	7 Jan 2021	Retrospective study (196 participants)		Procalcitonin (PCT), proadrenomedullin (pro-ADM) copeptin, CRP	Elevated copeptin was an indicator of one-year mortality (OR, 2.55; 95% CI: 1.18–5.54; $P=0.017$), and elevated pro-ADM was a predictor of in-hospital mortality (odds ratio [OR], 3.29; 95% CI: 1.04–11.5; $P=0.042$).
Chen *et al.*[3]	10 June 2020	case–control prospective study (five patient sample)	Sengenics Immunome Protein Array	GAPDH and DBNL	DBNL and GAPDH have a penetrance fold change of 26.120 and 5.667, respectively, and a penetrance percentage frequency of 33.333 and 66.667%, respectively, between IE patients and healthy controls, respectively
Bertolino *et al.*[37]	16 April 2022	Retrospective study (337 patient sample)		N-terminal prohormone brain natriuretic peptide	In 247 individuals with valvular IE, the median NT-proBNP level was 1500 pg/ml, which is significantly greater than in IE from other aetiologies.
Vollmer *et al.*[38]	2 Oct 2008	case–control prospective study (152 participants-57 IE patients,40 noninfectious heart valve disease,55 healthy patients)	IMMULITE LBP, Diagnostics Product Corporation/ Siemens Healthcare Diagnostics	Lipopolysaccharide binding protein	In IE patients, a correlation research found a strong correlation between LBP concentration and CRP concentrations ($r=0.70$; $P=0.0001$) and a moderate correlation between LBP concentration and WBC count ($r=0.33$; $P=0.001$). Weak correlations between CRP concentration and WBC count were observed ($r=0.26$; $P=0.05$).
Snipsøyr *et al.*[4]	21Sept 2015	216 IE cases out of 1006 patients		Procalcitonin, NT-proBNP, Cystatin C, LBP, Troponins,S100 calcium binding protein A11, Aquaporin-9(AQP9), Adhesion molecules, Interleukin-6	In comparison to controls, IE patients had greater troponin and PCT levels (6.56 ng/ml vs. 0.44 ng/ml), as well as higher NT-proBNP levels (4133 pg/ml) upon admission. Additionally, higher levels of VCAM-1 (1745 ng/ml vs. 1172 ng/ml), E-selectin (156 ng/ml vs. 80 ng/ml), and AQP9 transcript expression were seen in IE patients.
Wei *et al.*[39]	25 Dec 2017	Prospective case–control study (698 patient sample)	Receiver- operating characteristic analysis	Monocyte to high-density lipoprotein cholesterol ratio (MHR)	For predicting in-hospital death, MHR > 21.3 was 74.4% sensitive and 57.6% specific. Long-term death (hazard ratio 2.29, 95% CI: 1.44–3.64, $P=0.001$) and hospital stay (odds ratio 3.98, 95% CI: 1.91–8.30, $P=0.001$)
Cao *et al.*[40]	13 February 2020	Prospective cohort (160 patients)	Multiplexed microfluidic immunoassay kits (Ella platform; ProteinSimple)	IL-17A, soluble E-selectin or IL-10	Positive blood cultures within five days of the positive index blood culture on appropriate antibiotic therapy are predictive of persistent bacteremia.After day 3, criteria for IL-17A and IL-10 detected 71% and 65% of IE patients, respectively.
Ai *et al.*[41]	9 July 2022	Retrospective study (237 patients)		ANCA	18.1% of people tested positive for ANCA, mostly c-ANCA/anti-PR3, and these people had more severe purpura, macrohematuria, proteinuria, acute kidney injury, and fast progressing glomerulonephritis ($P=0.004$,.015,.043, and.043 proteinuria, respectively).
Mueller *et al.*[42]		Prospective cohort (67 patients - 12 confirmed IE)	TRACE technology (Kryptor-PCT)	Procalcitonin	During the initial admission, procalcitonin levels were the only significant predictor of IE ($P=0.018$)
SnipsØyr *et al.*[5]		(696 patients - 102 definite IE)	2D-PAGE and LFQ LC-MS/MS	Fibulin, Osteoprotegerin (OPG)	OPG levels were significantly greater in IE patients when compared to persons without the condition.
Kahveci *et al.*[43]		(45 patients with IE)		NT-pro-BNP cTnI	1. In IE patients, NT- pro-BNP levels have prognostic value. 2. NT-pro-BNP levels at initial presentation and cTnI levels help the risk assessment.
Martin *et al.*[1]			LS-MS/MS TAILS	Proteolytic peptides in fibronectin Complement C3	The peptides identified were abundant in vegetation and thus could be used as a marker for IE.
Zaratzian *et al.*[44]		(651 patients with suspected IE)		Antiphospholipid antibodies – anticardiolipin antibodies (IgG aCL)	Patients with confirmed IE had significantly elevated mean levels of aCL compared to those with suspected IE.

2D-PAGE, 2-dimensional polyacrylamide gel electrophoresis; AQP9, aquaporin-9 gene; CCL4, C-C motif chemokine ligand; CRP, C-reactive protein; cTnI, cardiac troponin I; DBNL, drebrin-like protein; ELISA, enzyme-linked immunosorbent assay; GADPH, glyceraldehyde-3-phosphate dehydrogenase; IL-15, Interleukin 15; IE, infective endocarditis; LFQ LC-MS/MS, label-free quantitative liquid chromatography-tandem mass spectrometry; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; qRT-PCR, quantitative real-time polymerase chain reaction; S100A11, S100 calcium-binding protein A11; TRACE, time-resolved amplified cryptate emission; TAILS, terminal amine isotopic labeling of substrates.

Microbiological diagnosis

The establishment of a diagnosis and the identification of organisms depend heavily on the results of positive blood cultures. *S. aureus* causes IE in 31% of cases, followed by *V. streptococci* (17% of cases), and *Enterococcus*[21,22].

Negative blood cultures do not rule out IE. Instead, *Bartonella*, *C. burnetii*, and *Tropheryma* are taken into consideration.

In an analysis of culture-negative endocarditis, serology identified the etiological bacterium in more than half of the cases, with the most common species being *C. burnetii* and *Bartonella*[23].

Imaging

All cases of suspected endocarditis require transthoracic echocardiography (TTE). TTE benefits as a first-line screening method by being quick, noninvasive, broadly accessible, and highly specific[24]. Patients with prosthetic valves see a 50% reduction in the sensitivity of TTE for detecting vegetation, whereas patients with electronic device implants experience a smaller reduction[25].

If the suspicion is still high regarding clinical criteria, in such instances with initially negative tests, a repeat TTE or TOE must be done after 5–7 days[26].

Additional imaging

Cardiac computed tomography (CT): This can be an excellent resource for those who have ambiguous echocardiogram results or conditions that preclude TOE. By recreating images of any segment, CT enables viewing from a variety of angles, regardless of the patient's morphology, or the operator's expertise[27].

Gahide *et al.*[28] reported a 71% sensitivity of CT in identifying vegetation. In the 'according to valve' analysis, Feutchner *et al.*[29] reported that CT had a 96% sensitivity and 97% specificity for surgical operation assessment.

Other imaging techniques that have been used include cardiac MRI and 18F-fluorodeoxyglucose PET-CT.

Clinical criteria

The Duke criteria, initially reported in 1994 and then revised in 2000, are used to diagnose IE[30,31].

Management and treatment

A committed team based in a reference center must oversee the management of IE. This should include cardiologists with a focus on coronary heart disease or cardiac imaging, infectious disease experts or microbiologists, cardiac surgeons, and experts in cardiac devices[32].

All patients should receive antibiotic therapy, and a few may benefit from surgery. For native valve infective endocarditis and prosthetic valve infective endocarditis (PVIE), the length of treatment varies from 2 weeks to 6 weeks.

Recommended therapy for common endocarditis causes

Oxacillin-susceptible patients are prescribed nafcillin or oxacillin, whereas oxacillin-resistant patients are given vancomycin or daptomycin for *S. aureus*[33]. For PVIE, vancomycin/oxacillin, rifampin, and gentamicin are used in combination. For those with *viridans Streptococcus*, parenteral penicillin, or ceftriaxone is used to treat penicillin-susceptible strains, while a combination of penicillin, gentamicin, and vancomycin is used to treat resistant bacteria. Patients with PVIE should receive either gentamicin or parenteral penicillin or ceftriaxone for the first two weeks of treatment. People who are allergic to gentamicin, ceftriaxone, or penicillin may benefit from using vancomycin.

Consideration is given to outpatient parenteral antibiotic therapy when people have a pathogenic organism that responds well to antibiotic therapy and who have a smooth course without problems after treatment[34].

IE may occasionally require surgery (valve repair, debridement, or valve replacement)[35].

Putative biomarkers for IE:

A higher pro-ADM level was a standalone indicator of in-hospital mortality (odds ratio, 3.29; 95% CI: 1.04–11.5; $P = 0.042$). A higher-than-normal level of copeptin was a reliable indicator of 1-year mortality (odds ratio, 2.55; 95% CI: 1.18–5.54; $P = 0.017$)[37] (Table 1).

A novel regulator in the signaling regulatory network of β-AR activation was identified as DBNL (also known as HIP-55). GAPDH was shown to be the main protein released by the endocarditis strain *S. gordonii* FSS2[38]. NT-proBNP median levels in staphylococcal IE were substantially greater than those in IE from other etiologies (1245.0 pg/ml; $P = 0.005$)[39].

It was observed that patients with heart valve disease had a diagnostic sensitivity of 96.7% for IE and a specificity of 87.5%, while healthy controls exhibited a diagnostic sensitivity of 94.5%. Combining the markers LBP and CRP resulted in a diagnostic sensitivity of 95.8% (95% CI: 92.2–99.4%) and a specificity of 87.5% (95% CI: 80.3–94.7%) when compared to healthy controls, with a diagnostic sensitivity of 97.3% (95% CI: 94.3–100.0%)[40].

IE patients exhibited elevated levels of LBP (33.41 mg/l vs. 6.67 mg/l), S100A11 protein (5.0 ng/ml vs. 2.1 ng/ml) compared to controls. Additionally, IE patients with acute heart failure showed increased mRNA levels of Aquaporin-9 (AQP9)[41].

During the study, a total of 44 hospital deaths (6.3%) occurred. The incidence of major adverse clinical events (MACEs) and in-hospital deaths showed an upward trend across the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) tertiles, with rates of 15.6, 20.9, and 30.6% for MACEs, and 3.9, 4.3, and 10.8% for in-hospital deaths. The predictive value of MHR for in-hospital death was similar to that of CRP, with AUC values of 0.670 and 0.702, respectively[42].

Higher levels of IL-17A, IL-10, and sE-selectin distinguish IE infection foci from extravascular infections in patients with IE infection foci identified by TEE or TTE imaging[43]. IE lasts longer, purpura happens more frequently, and the kidneys are harmed when antineutrophil cytoplasmic antibody (ANCA) is present[1]. Procalcitonin levels were the sole reliable indicator of IE in a study on 21 patients with IE verified by DUKE criteria[44]. Osteoprotegerin levels were shown to be elevated in IE patients in a different investigation, but their use as a sole diagnostic marker was constrained by its low sensitivity and specificity[45].

Few studies evaluated prognostic indicators for IE, like the one by Kahveci *et al.*[43], which concluded that the admission NT-proBNP can be a prognostic indicator for IE and, combined with cTnI, had a more significant value for risk stratification. Proteolytic peptides in fibronectin and complement C3 could be used as a potential biomarker for IE, Martin *et al.*[1]study concludes. Another study found that anticardiolipin antibodies

(IgG aCL) are elevated in definite IE and thus could help diagnose complex cases of IE[47].

Clinical implications

Serum proteome analysis may help identify potential novel IE biomarkers, which could have important clinical ramifications. These biomarkers may increase the speed and accuracy of IE diagnosis, enabling the early start of the appropriate course of therapy and possibly lowering overall mortality. Additionally, IE consequences including damaged valves, which may eventually necessitate surgical intervention, can be avoided with early identification[45]. According to a study, the discovery of diagnostic biomarkers like GAPDH and DBNL can help with the early detection of IE and function as useful diagnostic tools[3].

According to the current literature, novel biomarkers have shown promising potential in predicting the prognosis of IE. As such, healthcare providers may want to consider including these biomarkers in their diagnostic and management protocols for patients with suspected or confirmed IE. By utilizing these innovative tools, clinicians may be able to better tailor treatment plans and potentially improve patient outcomes.

According to a study by[46], a high prevalence of ANCA was found in patients diagnosed with IE, suggesting that aggressive therapy may be required to improve outcomes. The study also observed that ANCA-positive patients diagnosed with IE had longer hospital admission durations. Another study[16] highlighted the significance of procalcitonin levels, which were significantly elevated in cases of endocarditis complicated by sepsis or septic shock, indicating its potential as a biomarker for severe infection. The involvement of interleukin-6 (IL-6), interleukin-8 (IL-8), and interferon-gamma (IFN-γ) as prognostic biomarkers in adverse outcomes of infective prosthetic valve endocarditis was indicated in a study[47]. Furthermore, elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with increased 1-year and in-hospital mortality rates in patients with IE[48]. Another study[49] emphasized the importance of cardiac troponin I levels as a prognostic marker in IE, as patients with elevated levels had a higher rate of fatal clinical outcomes compared to those with normal levels. Additionally, elevated serum levels of interleukin-21 (IL-21) were found to be associated with severe valvular damage, including rupture of chordae tendineae, in patients with IE, indicating its potential as a biomarker for assessing the severity of valvular damage[50].

The identification of new biomarkers for IE has important clinical implications, particularly in their ability to distinguish IE from other diseases with similar symptoms. This differentiation is crucial, as it can lead to more appropriate treatment regimens.

Antiphospholipid antibodies (aPL) can develop on their own or in association with additional illnesses. In patients with definite IE compared to those with probable or rejected IE, aPL has been reported to be much more frequently positive and at greater levels. As a result, aPL may provide helpful in problematic IE diagnosis cases when it may be challenging to distinguish the condition from other illnesses. Utilizing aPL as a diagnostic tool may result in an earlier and more accurate diagnosis and suitable treatment, eventually improving patient outcomes[44].

One potential application of biomarkers in IE is to analyze the progression of the disease and evaluate the effectiveness of treatment. Patients with IE require continuous monitoring for possible relapses or complications, which can be time-consuming and costly. Biomarkers provide a noninvasive and cost-effective method to assess the patient's response to treatment and predict outcomes[51].

For instance, a study found that the IFN-γ/IL-2 ratio initially increased but declined to very low values from 5 months after the start of treatment, suggesting a successful treatment outcome. On the other hand, the ratio did not decrease significantly when treatment failed. Therefore, the use of biomarkers could help clinicians tailor treatment plans and improve patient outcomes by detecting early treatment failures and providing the necessary adjustments to avoid potential complications[52].

The studies mentioned have some limitations that need to be considered

More research is needed to validate the clinical usefulness of the identified biomarkers, including NT-proBNP, LBP, troponins, Cys C, AQP9, S100A11, CD54, CD62E, and IL-6, in larger patient populations with diverse clinical backgrounds. Therefore, these biomarkers should be further investigated in large-scale validation studies to confirm their prognostic and diagnostic value in clinical settings.

Standardization of sample collection, handling, and analysis is crucial to ensure the successful translation of these biomarkers into routine clinical practice. Therefore, it is important to establish standard protocols and procedures for sample collection, handling, and analysis to reduce variation in the results obtained from different laboratories and to ensure accurate and reliable biomarker measurements.

In unselected individuals with a diagnosis of IE in internal medicine, the study discovered a high incidence of ANCA. The pathogenicity of ANCA in IE has not yet been proven through study, though. To clearly demonstrate the function of ANCA in IE patients, more study is required. However, ANCA-positive IE can clinically resemble AAV, emphasizing the significance of a precise diagnosis and distinction between the two diseases.

Conclusion

This narrative review highlights novel recognized biomarkers for IE through serum proteomic analysis for IE, which can have significant clinical implications. Serum proteomics is a rapidly evolving field that can play an important role in improving the diagnosis and management of IE. By integrating serum proteomics with other clinical and imaging modalities, clinicians can enhance the accuracy and sensitivity of IE diagnosis and monitoring. Extensive studies are necessary for validating the clinical importance of these novel biomarkers by serum proteomic analysis for IE and standardize the collection, handling, and analysis of samples. Once these steps are taken, these biomarkers can be integrated into daily clinical practice, enhancing the diagnosis and management of IE.

Ethical approval

This is a narrative review article hence ethics approval was not required for it.

Consent

Informed consent was not required for this review.

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Author contribution

A.B.: conceived the concept of study, did study designing and manuscript writing; S.M., S.S., D.K., A.V., and M.M.: literature search and manuscript writing; J.K.: manuscript editing, drafting, and proofreading; A.L.B., R.W.B., H.S.M., and M.S.: manuscript editing and drafting; K.A.: manuscript editing, drafting, proofreading, and final approval of the manuscript.

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The authors declare that they have no financial conflicts of interest with regard to the content of this report.

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