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The predictive value of endocan as a novel biomarker: an umbrella study on meta-analyses

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Abstract

Background and aim In recent years, endocan has emerged as a potential biomarker in various medical conditions. This multifaceted molecule, involved in key processes such as inflammation and endothelial dysfunction, has shown promise in predicting disease progression and therapeutic response across a spectrum of pathologies. However, the heterogeneity of studies and the complexity of endocan's role in different diseases necessitate a comprehensive review. This umbrella review aimed to systematically synthesize and evaluate the evidence from multiple meta-analyses, offering a view of endocan's effectiveness as a predictive biomarker in medical diseases.

Methods An extensive search was carried out on March 12, 2024, using the following four databases: PubMed, Scopus, Web of Science, and Cochrane Library. The goal was to identify meta-analyses that assess endocan's predictive efficacy. The pooled effect size and its 95% confidence interval were taken out of each discovered meta-analysis. Furthermore, power analyses were performed to assess the robustness and dependability of the results. An additional GRADE assessment was carried out to gauge the epidemiological reliability of the findings.

Results In the final analysis, 12 meta-analyses were included in the current umbrella review. The results showed that there is a significant correlation between a higher endocan level and COVID-19 (SMD: 1.40, 95% CI 0.21–2.58, $P=0.02$), followed by chronic kidney disease (SMD: 1.34, 95% CI 0.20 to 2.48, $P<0.01$), obstructive sleep apnea (SMD: 1.30, 95% CI 1.06–1.54, $P<0.01$), diabetes mellitus (SMD: 1.00, 95% CI 0.81 to 1.19, $P<0.01$), coronary artery disease (SMD: 0.99, 95% CI 0.58–1.39, $P<0.01$), hypertension (SMD: 0.91, 95% CI 0.44–1.38, $P<0.01$), and preeclampsia (SMD: 0.37, 95% CI 0.13–0.62, $P<0.01$).

Conclusion Endocan has emerged as a highly promising biomarker with considerable potential across various medical conditions. Its relevance spans critical areas such as COVID-19, chronic kidney disease, obstructive sleep apnea, diabetes mellitus, coronary artery disease, and preeclampsia. The broad applicability of endocan highlights its value in improving diagnostic accuracy and enhancing our understanding of these diseases. Clinically, incorporating endocan testing could aid in early detection, monitoring disease progression, and refining patient management, particularly for high-risk populations. However, additional research is needed to fully assess its specificity, sensitivity, and overall clinical utility, paving the way for its integration into routine healthcare practices and enabling more precise, individualized treatment strategies.

Keywords Cardiovascular outcome, Clinical performance, Endocan, Meta-analysis, Prediction, Systematic review, Umbrella review

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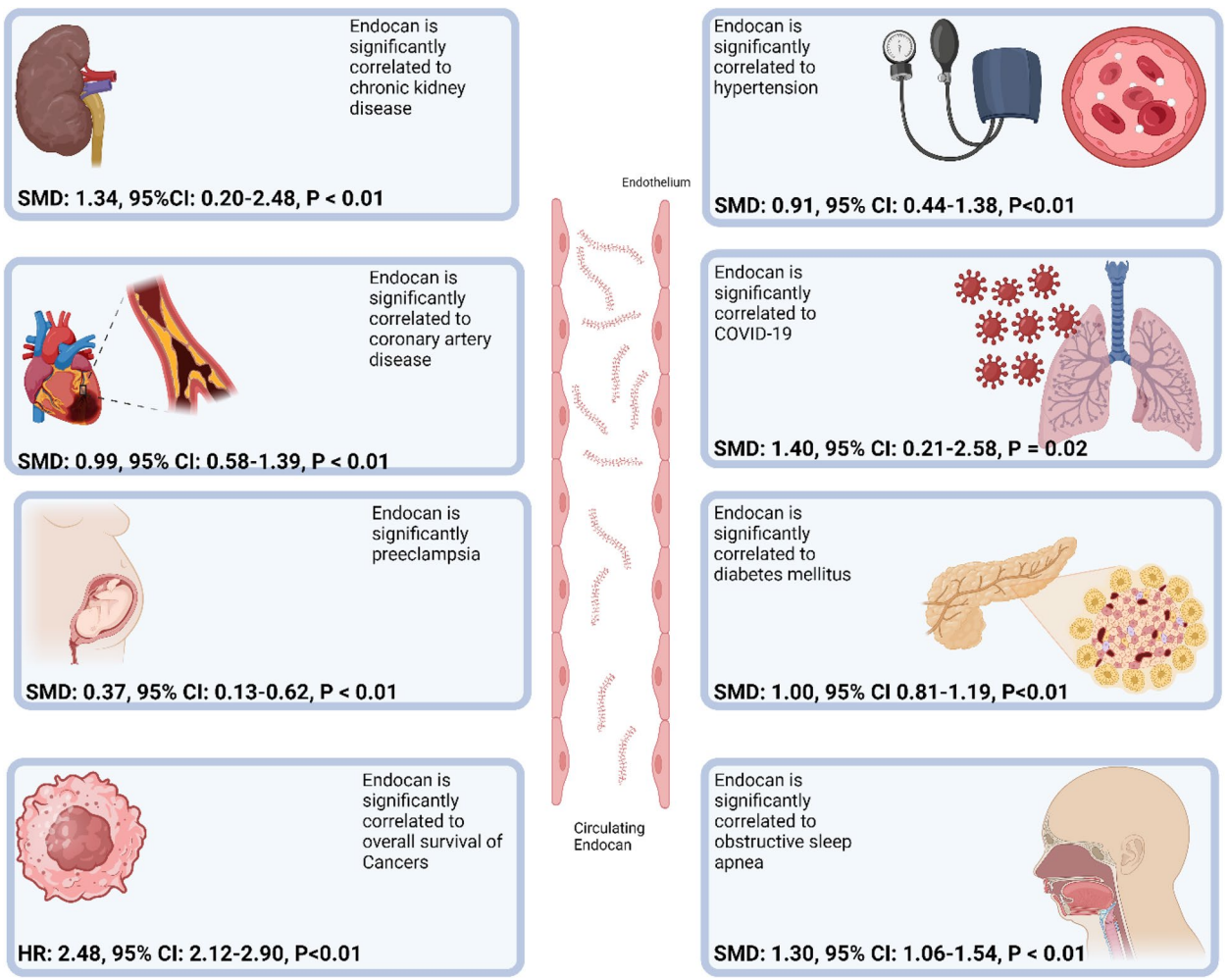
Graphical Abstract



Introduction

In recent years, the identification of novel biomarkers has emerged as a pivotal area of research, offering new possibilities for improving disease diagnosis, prognosis, and therapeutic interventions [1, 2]. Among these, endocan, also known as endothelial cell-specific molecule 1 (ESM-1), has garnered significant attention due to its role as a soluble proteoglycan synthesized by vascular endothelial cells [3, 4]. Its involvement in key processes such as endothelial dysfunction, inflammation, and angiogenesis makes it a promising biomarker for a wide array of clinical applications [5–9].

Endocan plays a critical role in vascular homeostasis, influencing endothelial cell adhesion, migration, and angiogenesis through receptor-mediated pathways [9, 10]. It also modulates the release of pro-inflammatory cytokines and chemokines, impacting systemic inflammatory responses [11]. These properties have linked endocan to the pathogenesis and progression of numerous conditions, including cancer, cardiovascular disease, sepsis, respiratory disorders, and renal dysfunction [9, 12–16]. Moreover, evidence from prior studies suggests that elevated endocan levels may correlate with disease severity, progression, and patient outcomes, highlighting its potential utility as a prognostic and predictive biomarker [3, 17–19].

Despite the growing body of research, existing evidence remains fragmented, with individual meta-analyses focusing on specific diseases or contexts [20–24]. This fragmented approach limits our ability to

draw overarching conclusions about endocan's predictive utility across multiple disorders. While these meta-analyses provide valuable disease-specific insights, a comprehensive synthesis of their findings is crucial to establish a broader understanding of endocan's clinical relevance and to address inconsistencies or heterogeneity in the evidence.

Our study aims to fill this gap by conducting an umbrella review of meta-analyses that have assessed endocan's predictive value across various diseases. By consolidating and evaluating the available evidence, we seek to provide a holistic perspective on the clinical applications of endocan. In addition to summarizing the evidence, we will assess the methodological quality of the included meta-analyses to determine the strength of the evidence base, offering a robust foundation for future research and clinical practice.

Methods

The guidelines outlined in the Cochrane Handbook for Systematic Reviews were adhered to in this review [25]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed in the reporting of findings [26]. A preregistration for the study plan was made in PROSPERO (CRD CRD42024519025).

Search strategy

Two independent researchers (S.N and S.H) developed a thorough search strategy to identify meta-analyses that evaluate the diagnostic significance of endocan in different diseases. This search formula was implemented in four databases (PubMed, Scopus, Cochrane Library, and Web of Science) from inception until March 12, 2024. An update to the search was conducted on January 23, 2025. The search terms utilized encompassed keywords like "Endocan," "ESM 1," "endothelial cell-specific molecule 1," "systematic reviews," and "meta-analysis." To enhance the accuracy of the search strategy, the assistance of two specialists was sought. Furthermore, a manual search of references from included studies was performed. Language limitations were not imposed. In cases of disagreement, a third researcher (E.AS) was consulted to reach a resolution. The organization and handling of the identified studies were facilitated using EndNote X20. The detailed search formula for each database is presented in Table S1.

Study selection and eligibility criteria

The selection of studies was carried out by two separate researchers (S.N and S.H). When disagreements arose, they resolved them via correspondence (E.AS). The meta-analyses included in the study had to meet the following criteria: they needed to assess endocan as a biomarker for a specific disease and focus on a particular condition in the study population. Original research, commentaries, editorials, and narrative reviews were excluded.

Quality assessment

AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, Version 2) is a widely recognized and validated tool for evaluating the methodological quality of systematic reviews and meta-analyses. AMSTAR 2 consists of 16 questions that help reviewers assess various aspects of a study's methodological rigor, including its design, conduct, and reporting [27]. It is commonly used in umbrella reviews, particularly for interventions, diagnostics, and prognostic studies [28–33].

Using the AMSTAR2 checklist 12, the methodological quality of the included meta-analyses was evaluated. The 16 questions on the checklist were used by two reviewers (S.N and S.H) to independently assess the studies. They gave answers of "yes," "no," or "partial yes." A third researcher (E.AS) was consulted to settle any disagreements among the reviewers. Based on the results of the checklist grading, four groups of meta-analyses could be identified: high quality, moderate quality, low quality, and critically low quality.

Data extraction

From the included studies, the following data were collected: First author's name, the year and publication journal, the medical condition of which endocan was evaluated, the effect size with a 95% confidential interval of the outcomes, heterogeneity assessments, publication bias information, the funding source for the research, the protocol registration number, and the quality assessment instrument utilized to evaluate the included studies' quality. Two researchers worked independently to extract the data (MH.K and R.N), and a third researcher resolved any discrepancies. We contacted the corresponding and primary authors to address any missing information.

Statistical analyses

The statistical analysis for this umbrella review was conducted by synthesizing the data from the included meta-analyses. The effect sizes across various medical conditions were assessed using standardized mean difference (SMD), odds ratio (OR), or hazard ratio (HR), depending on the outcome reported by included studies. The selection criterion in cases where two or more meta-analyses assessed a shared medical condition was based on the meta-analysis with the highest sample size.

Power analysis was also performed to assess the adequacy of the sample sizes in the included meta-analyses. This analysis ensures that the studies were sufficiently

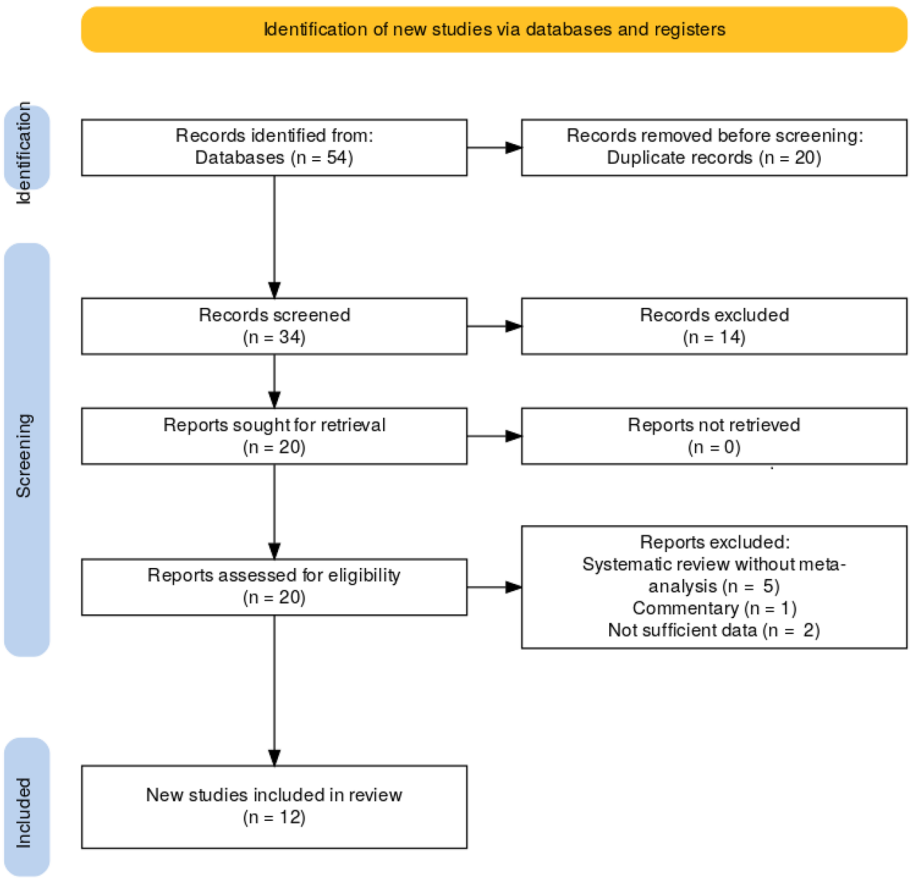


Fig. 1 Study selection process

powered to detect significant effects. The robustness of the results was further evaluated through a GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) assessment, which was used to determine the quality of the evidence for each outcome. GRADE categorizes the quality of evidence into four levels: high, moderate, low, and very low. The quality of evidence was considered high when there was strong confidence in the results, moderate when there were some concerns but the results remained reliable, and low or very low when there were serious concerns regarding study design or risk of bias. Grade assessment was conducted using the GRADE profiler version 3.6. All statistical analyses were carried out using Comprehensive Meta-Analysis (CMA) software version 4.

Results

During the initial search phase, a total of 54 studies were identified and sourced from various databases: 12 from PubMed, 24 from Scopus, and 18 from Web of Science. No relevant studies were found in the Cochrane Library. After removing 20 duplicate entries and reviewing the titles and abstracts of the remaining articles, 20 studies proceeded to a comprehensive full-text evaluation. Ultimately, following this thorough assessment, 12 studies met the criteria for inclusion in the umbrella review. A visual representation of the study selection process is provided in Fig 1.

Study characteristic

A total of 12 meta-analyses were ultimately incorporated into the present umbrella review, encompassing publication dates from 2016 to 2024. The range of studies included and the overall sample size demonstrated variability, with original study counts ranging from 4 to 24 and participant numbers spanning from 767 to 3354, respectively. This assessment covered 11 medical conditions, encompassing diabetes mellitus, overall survival and recurrence-free survival of cancer, hypertension (HTN), preeclampsia, coronary artery disease (CAD), coronary slow flow (CSF), obstructive sleep apnea (OSA), sepsis, chronic kidney disease (CKD), acute respiratory distress syndrome (ARDS), and coronavirus disease 2019

Table 1 Characteristics of included studies

First author name, year of publication	Journal	Searched databases	Date of search	Number of included studies	Total sample size	Outcome	Checklist used for quality assessment of included original studies	Funding status	Previous registered protocol	Model of analysis	AMSTAR 2 score
Khalaji, 2023 [20]	Diabetology & Metabolic Syndrome	PubMed, Web of Science, Scopus, and Embase	February 13, 2023	24	3354	Diabetes mellitus	Newcastle–Ottawa quality assessment scale	No	No	Random-effect meta-analysis	Low quality
Huang, 2016 [21]	OncoTargets and Therapy	PubMed, Embase, and China National Knowledge Infrastructure	September 22, 2015	15	1,464	Overall survival and recurrence-free survival of cancer	Newcastle–Ottawa quality assessment scale	Natural Science Foundation of China (81672869), National Science Foundation for Young Scholars (81,302,013), Jiangsu Provincial Science Foundation (BK20161596), and Jiangsu Provincial Six talent peak of Human affair Hall Funding (2013-WSW-037)	No	random-effect model or a fixed-effect model regarding the heterogeneity of the results	Low quality
Behnoush, 2023[22]	Hypertension Research	PubMed, Scopus, Embase, and Web of Science	February 8, 2023	20	3130	Hypertension	Newcastle–Ottawa quality assessment scale	Not reported	No	Random effect model	Low quality
Lan, 2020 [23]	Bioscience Reports	PubMed and Embase	June 25, 2019	8	893	Preeclampsia	Newcastle–Ottawa quality assessment scale	No funding	No	random-effect model or a fixed-effect model regarding the heterogeneity of the results	Low quality
Zhao, 2018 [24]	Medicine (Baltimore)	PubMed, Embase, Cochrane Library, SinoMed, and Web of Science,	June 1, 2018	15	3097	Coronary artery disease, coronary slow flow	Newcastle–Ottawa quality assessment scale	Hubei Provincial Department of Education (D20171201), Research Fund for Excellent Dissertation of China Three Gorges University (2017YPY060), and National Science Foundation of China grant (5281200)	No	random-effect model or a fixed-effect model regarding the heterogeneity of the results	Critically Low quality
He,2023 [34]	Medicine (Baltimore)	PubMed, Cochrane Library, China National Knowledge Infrastructure, Web of Science, Embase, and Wan Fang database	January 2000 up to June 10, 2023	12	2199	Obstructive sleep apnea	Newcastle–Ottawa quality assessment scale	Sichuan Medical Research Project Foundation (grant number: S21054) and Priming Scientific Research Foundation (CYFY-GQ59)	Prospero (CRD42023433137)	random-effect model or a fixed-effect model regarding the heterogeneity of the results	Low quality
Behnoush, 2023 [37]	Angiology	PubMed, Embase, Web of Science, and Scopus	February 2023	7	1390	Obstructive sleep apnea	Newcastle–Ottawa quality assessment scale	No funding	No	Random effect model	Low quality

Table 1 (continued)

First author name, year of publication	Journal	Searched databases	Date of search	Number of included studies	Total sample size	Outcome	Checklist used for quality assessment of included original studies	Funding status	Previous registered protocol	Model of analysis	AMSTAR 2 score
Fernández-Sarmiento, 2023 [38]	journal of intensive care medicine	Cochrane library, PubMed/MEDLINE, Embase, LILACS and Google Scholar	December 31, 2021	6	1,132	sepsis	Newcastle–Ottawa quality assessment scale	No funding	Prospero (CRD42020217935)	random-effect model or a fixed-effect model regarding the heterogeneity of the results	Low quality
Khalaji, 2023 [15]	Plos One	PubMed, Embase, Scopus, and Web of Science	February 13, 2023	20	2316	Chronic kidney disease	Newcastle–Ottawa quality assessment scale	No funding	Prospero (CRD42023423593)	Random effect model	High quality
Zhan, 2023 [35]	Therapeutic Advances in Respiratory Disease	PubMed, EMBASE, and the Cochrane Library	1 December 2019 up to 18 May 2023	11	767	Covid-19	Newcastle–Ottawa quality assessment scale	National Natural Science Foundation of China (82373,643), Chongqing Talents: Exceptional Young Talents Project (CQYC202005003), Outstanding Youth Science Foundation of Chongqing (cstc2020jcyj-jqX0014), and the Science Foundation for Outstanding Young People of the Army Medical University	No	Random-effect model or a fixed-effect model regarding the heterogeneity of the results	Low quality
Gaspar, 2022 [36]	Sleep Medicine Reviews	PubMed/Medline, Cochrane Library, Biblioteca Virtual da Saúde, Web of Science, EMBASE, World Intellectual Property Organization database, and bioRxiV and medRxiV Preprint Servers	May 31 st, 2020	16	2156	Obstructive sleep apnea	Quality Assessment Tool for Diagnostic Accuracy Studies	European Regional Development Fund (ERDF), through the Centro 2020 Regional Operational Programme, under the project CENTRO-01–0145-FEDER-000012 (HealthyAging 2020); through the Operational Programme for Competitiveness and Internationalisation (COMPETE 2020) and Portuguese national funds via Fundaç ~ao para a Ci^encia e a Tecnologia (FCT), under the projects POCI-01–0145-FEDER-029002 (noOSAnoAGEING, PTDC/MEC-MCI/29002/2017), UIDB/04539/2020, UIDP/04539/2020 and LA/P/0058/2020; and by the Euro	Prospero (CRD42020132556)	Random effect model	High quality

Table 1 (continued)

First author name, year of publication	Journal	Searched databases	Date of search	Number of included studies	Total sample size	Outcome	Checklist used for quality assessment of included original studies	Funding status	Previous registered protocol	Model of analysis	AMSTAR 2 score
								pean Social Fund through the Human Capital Operational Programme (POCH) and Portuguese national funds via FCT under PD/BD/135497/2018, COVID/BD/152507/2022, 2020.04499.BD, and 2021.05334.BD			
Behnoush, 2024 [39]	Health Science Reports	PubMed, SCOPUS, Embase, and Web of Science	March 24, 2023	14	1058	Acute respiratory distress syndrome	Newcastle–Ottawa quality assessment scale	No funding	No	Random effect model	Low quality

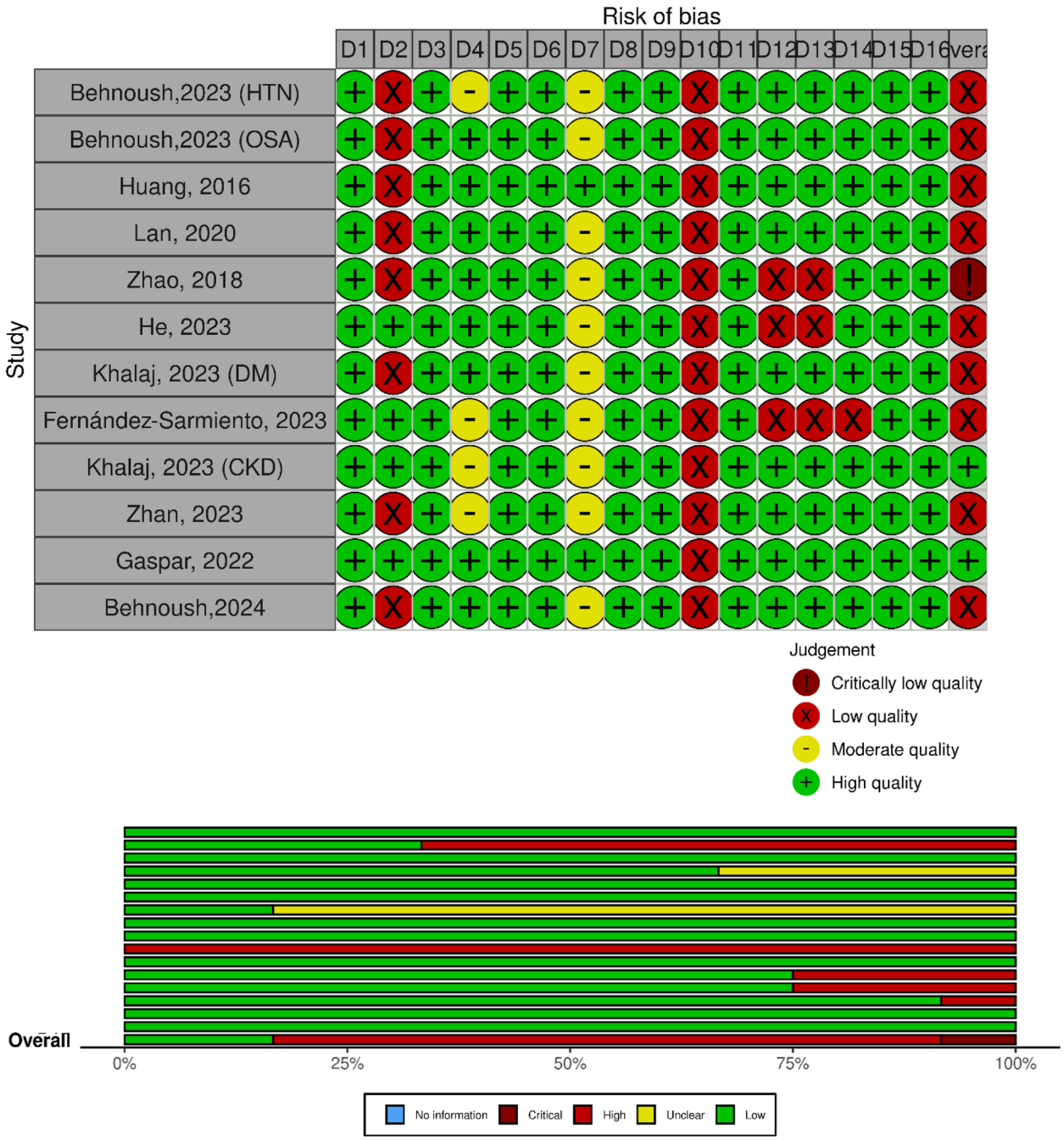


Fig. 2 Quality assessment of included studies based on AMSTAR2 checklist

(COVID-19), conducted by the meta-analyses featured in this review. Funding information indicated that five studies received financial support [21, 24, 34–36], while the remainder lacked financial sponsorship [15, 20, 22, 23, 37–39]. According to the AMSTAR2 checklist, one study was considered as critically low quality [24], nine were rated as low quality [20–23, 34, 35, 37–39], and two were assessed as high quality [15, 36]. Only four studies reported a previously registered protocol in PROSPERO [15, 34, 36, 38], whereas the remaining seven studies lacked information on a registered protocol [20–24, 35, 37, 39]. Table 1 presents a summary of all the studies that have been included. Details on evaluating the quality of the included studies are given in Fig. 2.

Table 2 Predictive value of endocan in various medical conditions

Variable	Predictive value with 95% CI interval	heterogeneity	*P* value of Begg's Publication bias	P value of Egger's publication bias	Power
Diabetes mellitus	SMD 1.00, 95% CI 0.81–1.19, $P < 0.01$	62.19%	0.24	0.60	1-b = 1
Overall survival of Cancers	HR: 2.48, 95% CI: 2.12–2.90, $P < 0.01$	25.80%	Not reported	0.46	–––––
Recurrence-free survival of cancers	HR: 2.08, 95% CI: 1.40–3.09, $P < 0.01$	0.00%	Not reported	0.37	–––––
Hypertension	SMD: 0.91, 95% CI: 0.44–1.38, $P < 0.01$	95.43%	0.49	0.02	1-b = 1
Preeclampsia	SMD: 0.37, 95% CI: 0.13–0.62, $P < 0.01$	65.00%	Not reported	0.41	1-b = 0.99
Coronary artery disease	SMD: 0.99, 95% CI: 0.58–1.39, $P < 0.01$	89.8%	0.36	Not reported	1-b = 1
Coronary slow flow	SMD: 0.62, 95% CI: 0.45–0.78, $P < 0.01$	0.00%	0.66	Not reported	1-b = 1
Obstructive sleep apnea	SMD: 1.30, 95% CI: 1.06–1.54, $P < 0.01$	81.3%	Not reported	0.07	1-b = 1
Sepsis mortality	OR: 9.53, 95% CI: 3.34–27.3, $P < 0.01$	78.00%	Not reported	Not reported	1-b = 1
Sepsis multiple organ dysfunction syndrome	OR: 8.33, 95% CI: 2.07–33.58, $P < 0.01$	83.00%	Not reported	Not reported	1-b = 1
Sepsis respiratory failure	OR: 9.66, 95% CI: 2.26–43.95, $P < 0.01$	73.00%	Not reported	Not reported	1-b = 1
Chronic kidney disease	SMD: 1.34, 95%CI: 0.20–2.48, $P < 0.01$	98.32%	Not reported	Not reported	1-b = 1
COVID-19	SMD: 1.40, 95% CI: 0.21–2.58, $P = 0.02$	95.00%	Not reported	> 0.05	1-b = 1
Acute respiratory distress syndrome	SMD: 0.47, 95% CI: 0.10–0.84, $P = 0.01$		Not reported	Not reported	1-b = 0.90

Findings

The predictive value of endocan in diabetes mellitus

In a comprehensive meta-analysis, Khalji et al. explored the prognostic significance of endocan levels in diabetic patients [20]. Their evaluation encompassed 24 studies involving 3354 subjects, revealing significantly elevated endocan levels in diabetic individuals (SMD: 1.00; 95% CI 0.81–1.19; $P < 0.01$) (Table 2). Notably, the subgroup analysis showed that diabetic patients without additional health conditions exhibited higher endocan levels compared to healthy controls (SMD: 1.03; 95% CI 0.79–1.28; $P < 0.01$). This trend was consistent even in diabetics with comorbidities, such as cirrhosis (SMD: 0.95; 95% CI 0.73–1.18; $P < 0.01$), coronary artery disease (SMD: 0.87; 95% CI 0.19–1.54; $P < 0.01$), and erectile dysfunction (SMD: 0.94; 95% CI 0.20–1.67; $P < 0.01$).

Furthermore, the study underscored a statistically significant elevation of endocan levels in type 2 diabetes patients (SMD: 1.01; 95% CI 0.78–1.24; $P < 0.01$). This increase was observed both in type 2 diabetics without comorbid conditions (SMD: 1.02; 95% CI 0.74–1.31; $P < 0.01$) and in those with additional health issues, including cirrhosis (SMD: 0.95; 95% CI 0.73–1.18; $P < 0.01$) and erectile dysfunction (SMD: 0.94; 95% CI 0.20–1.67; $P < 0.01$).

The predictive value of endocan in cancers

In a meta-analysis conducted by Huang et al., the study aimed to evaluate the prognostic significance of endocan levels in various cancers [21]. This extensive review incorporated data from 15 studies, encompassing a total of 1464 participants. The findings revealed that elevated endocan levels are associated with significantly decreased overall survival among cancer patients, with a hazard ratio (HR) of 2.48 (95% CI 2.12–2.90; $P < 0.01$) (Table 2). Further detailed analyses within specific cancer subgroups demonstrated that increased endocan expression serves as a detrimental prognostic factor in both gastrointestinal cancers (HR 2.27; 95% CI 1.77–2.91; $P < 0.01$) and hepatocellular carcinoma (HR 2.61; 95% CI 1.96–3.48; $P < 0.01$). Moreover, the study highlighted that high endocan levels are predictive of poorer recurrence-free survival, evidenced by a pooled HR of 2.08 (95% CI 1.40–3.09; $P < 0.01$) (Table 2).

The predictive value of endocan in hypertension

In a comprehensive meta-analysis comprising 20 studies and 3130 participants, Behnoush et al. explored the correlation between endocan levels and HTN [22]. Their investigation revealed that individuals with HTN exhibited elevated circulating endocan levels (SMD: 0.91; 95% CI 0.44–1.38; $P < 0.01$) in comparison to healthy controls (Table 2). Further subgroup analysis disclosed a significant elevation in serum endocan levels among hypertensive subjects compared to normotensive individuals (SMD: 1.02; 95% CI 0.45–1.58; $P < 0.01$). However, findings from the plasma subgroup did not demonstrate statistical significance (SMD: 0.50; 95% CI −0.19–1.18; $P = 0.15$).

To mitigate the influence of comorbidities on endocan levels among hypertensive patients, the authors excluded individuals with underlying conditions. Notably, their

results revealed statistically higher endocan levels among hypertensive patients without underlying conditions (SMD: 1.16; 95% CI 0.66–1.65; $P < 0.01$) compared to their normotensive counterparts.

The predictive value of endocan in preeclampsia

In a comprehensive meta-analysis encompassing 8 studies and involving 893 individuals, Lan et al. examined the predictive significance of endocan in the context of preeclampsia [23].

The meta-analysis outcomes revealed that women experiencing preeclampsia exhibited significantly elevated circulating levels of endocan compared to those with uncomplicated pregnancies (SMD: 0.37; 95% CI 0.13–0.62; $P = 0.003$) (Table 2).

Interestingly, subgroup analyses provided distinctive insights. Among these, it was observed that women with late-onset preeclampsia manifested significantly higher levels of circulating endocan compared to those with normal pregnancies (SMD: 0.25; 95% CI 0.01–0.49; $P = 0.04$). However, this distinction diminished when comparing early-onset preeclampsia with normal controls (SMD: 0.30; 95% CI −0.08–0.69; $P = 0.12$).

Furthermore, the study highlighted the impact of maternal age on the interplay between endocan and preeclampsia. Notably, the association between endocan levels and preeclampsia differed significantly based on maternal age. For women aged 29 and above, there was no significant disparity in endocan levels between preeclampsia and normal delivery (SMD: 0.09; 95% CI −0.13–0.32). Conversely, among women below the age of 29, those with preeclampsia demonstrated markedly higher endocan levels compared to their counterparts with normal deliveries (SMD: 0.58; 95% CI 0.22–0.93; $P = 0.001$).

The predictive value of endocan in coronary artery diseases

A thorough meta-analysis involving 15 studies and 3097 participants was conducted by Zhao et al. [24]. The primary objective of the analysis was to explore the potential role of endocan in cardiovascular diseases. The results of their investigation demonstrated a clear link between CAD and serum endocan levels. Serum endocan levels were significantly higher in CAD patients than in non-CAD subjects (SMD: 0.99; 95% CI 0.58–1.39; $P < 0.01$) (Table 2).

According to the study, blood endocan levels were also significantly greater in CAD patients with hypertension compared to patients with hypertension alone (SMD: 0.61; 95% CI 0.30–0.92; $P < 0.01$). Furthermore, the results of the meta-analysis were applicable to cases with CSF, indicating a substantial difference in serum endocan levels between those with SCF and controls with normal coronary flow (NCF) (SMD: 0.62; 95% CI 0.45–0.78; $P < 0.01$).

The predictive value of endocan in OSA

In a comprehensive meta-analysis conducted by He et al., twelve studies were examined to assess the correlation between endocan levels and OSA [34]. This analysis revealed that patients with OSA exhibited markedly higher levels of serum/plasma endocan than healthy individuals, with an SMD of 1.30 (95% CI 1.06–1.54; $P < 0.01$) (Table 2).

Subgroup analysis focusing on the association between endocan levels and the severity of OSA demonstrated that individuals with mild OSA had elevated endocan levels compared to controls (SMD: 1.07; 95% CI 0.79–1.36; $P < 0.01$). Similarly, those with moderate OSA also showed increased serum/plasma endocan levels (SMD: 1.33; 95% CI 1.00–1.65; $P < 0.01$), and this trend was even more pronounced in severe OSA cases (SMD: 1.53; 95% CI 0.97–2.09; $P < 0.01$).

The meta-analysis also highlighted the predictive role of endocan levels in OSA across different body mass index (BMI) categories. Specifically, individuals with a BMI over 30 had an SMD of 1.34 (95% CI 0.96–1.72; $P < 0.01$), while those with a BMI under 30 had an SMD of 1.24 (95% CI 1.03–1.46; $P < 0.01$). Both serum and plasma endocan levels were significantly higher in OSA patients, with serum endocan at SMD: 1.33 (95% CI 1.02–1.65; $P < 0.01$) and plasma endocan at SMD: 1.19 (95% CI 1.00–1.38; $P < 0.01$).

Interestingly, the study also found a connection between endocan levels and the apnea–hypopnea index (AHI), a crucial metric for assessing the severity of OSA. AHI and endocan levels exhibited a moderately positive correlation (COR: 0.69; 95% CI 0.36–1.02; $P < 0.01$). Furthermore, there was a moderate negative association (COR: −0.68; 95% CI −0.82 to −0.55; $P < 0.01$) between serum endocan levels and flow-mediated dilation (FMD). Additional findings included a mild positive correlation (COR: 0.47; 95% CI 0.05–0.90; $P < 0.01$) between serum endocan levels and carotid intima-media thickness (CIMT), and a moderate negative correlation (COR: −0.34; 95% CI −0.53 to −0.15; $P < 0.01$) between minimum oxygen saturation and endocan levels.

Predictive value of endocan in sepsis

Fernández-Sarmiento et al. undertook a study to explore the significance of endocan in predicting the prognosis of patients with sepsis. Their meta-analysis encompassed 6 studies, involving a total of 1132 individuals [37]. The findings of their investigation revealed that endocan holds promise as a prognostic indicator in sepsis, as individuals with elevated levels of endocan exhibited a

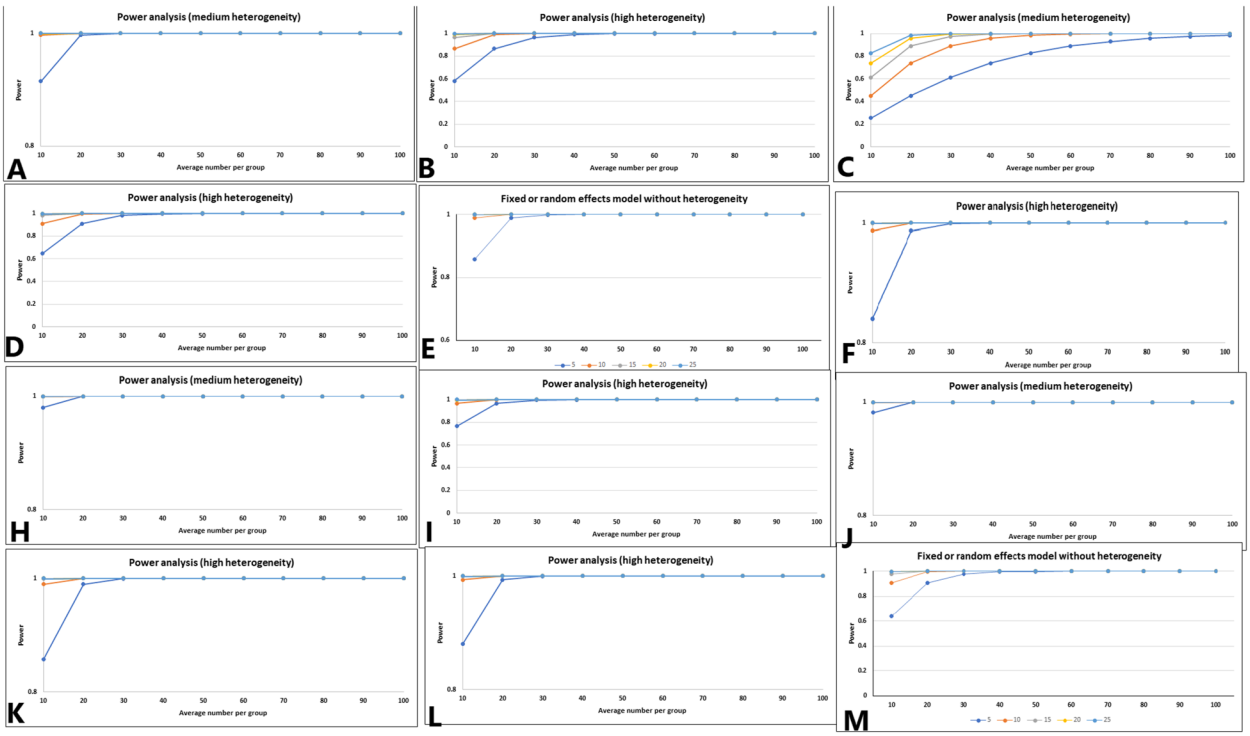


Fig. 3 Results of power analysis. **A** Diabetes mellitus. **B** Hypertension. **C** Preeclampsia. **D** Coronary artery disease. **E** Coronary slow flow. **F** Obstructive sleep apnea. **G** Sepsis mortality. **H** Sepsis multiple organ dysfunction syndrome. **I** Sepsis respiratory failure. **J** Chronic kidney disease. **K** COVID-19. **L** Acute respiratory distress syndrome

significantly heightened risk of mortality (OR 9.53; 95% CI 3.34–27.3; $P < 0.01$) (Table 2).

Moreover, patients with higher levels of this biomarker were observed to have an increased likelihood of developing multiple organ dysfunction syndrome (OR 8.33; 95% CI 2.07–33.58; $P < 0.01$) and respiratory failure (OR 9.66; 95% CI 2.26–43.95; $P < 0.01$) (Table 2).

Predictive value of endocan in chronic kidney disease

A comprehensive examination of the correlation between endocan and CKD was conducted in Khalaji et al.'s investigation [15]. Their extensive meta-analysis included data from 20 trials involving a total of 2316 participants. The findings revealed that circulating endocan levels were significantly higher in patients with CKD (SMD: 1.34; 95% CI 0.20–2.48; $P < 0.01$) (Table 2).

Subgroup analysis focusing on serum and plasma endocan levels found a strong association between CKD and plasma endocan levels (SMD: 0.71; 95% CI 0.34–1.00; $P < 0.01$). Conversely, no statistically significant difference was observed in the serum endocan subgroup analysis (SMD 2.02; 95% CI −0.31 to 4.34; $P = 0.09$).

To minimize the potential impact of underlying conditions on serum endocan levels, the authors excluded patients with comorbidities. They found that patients without such conditions had significantly higher endocan levels compared to the control group (SMD 0.74; 95% CI 0.52–0.95; $P < 0.01$).

The predictive value of endocan in COVID-19

In a recent meta-analysis conducted by Zhan et al., the predictive value of endocan in COVID-19 patients was assessed [35]. The study revealed that higher levels of endocan were observed in COVID-19 patients upon admission compared to the control group (SMD 1.40; 95% CI 0.21–2.58; $P = 0.02$) (Table 2). Additionally, it was found that higher endocan levels at admission were observed in poor prognosis groups compared to the control group (SMD 0.64; 95% CI 0.29–0.99; $P < 0.01$).

The predictive value of endocan in acute respiratory distress syndrome

A recent study by Behnoush et al. explored the potential of endocan as a biomarker for ARDS [39]. The analysis included 14 studies with a total of 1058 patients, comparing endocan levels in ARDS patients to non-ARDS controls.

The results revealed significantly higher endocan levels in patients developing ARDS compared to those without the condition (SMD 0.47; 95% CI 0.10–0.84; $P = 0.01$)

Table 3 GRADE assessment of the predictive value of endocan in different medical conditions

Quality assessment							Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Diabetes mellitus							
24	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	Strong association	Low
Overall survival of cancers							
14	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association	Moderate
Recurrence-free survival of cancers							
3	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Low
Hypertension							
20	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	Reporting bias very strong association	Low
Preeclampsia							
3	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None	Very low
Coronary artery disease							
8	Observational studies	Serious	Very serious	No serious indirectness	No serious imprecision	Very strong association	Very low
Coronary slow flow							
3	Observational studies	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	Very low
Sepsis mortality							
6	Observational studies	Serious	Serious	No serious indirectness	No serious imprecision	Very strong association	Low
Sepsis multiple organ dysfunction syndrome							
3	Observational studies	Serious	Very serious	No serious indirectness	No serious imprecision	Very strong association	Very low
Sepsis respiratory failure							
3	Observational studies	Serious	Serious	No serious indirectness	No serious imprecision	Very strong association	Low
Chronic kidney disease							
20	Observational studies	No serious risk of bias	Very serious	No serious indirectness	No serious imprecision	Strong association	Very low
COVID-19							
11	Observational studies	No serious risk of bias	very serious	No serious indirectness	No serious imprecision	Strong association	Very low
Obstructive sleep apnea							
12	Observational studies	Serious	Very serious	No serious indirectness	No serious imprecision	Strong association	Very low

(Table 2). Moreover, endocan levels were found to be higher in ARDS non-survivors compared to survivors (SMD 0.31; 95% CI 0.02–0.60; $P = 0.03$).

Results of power analysis

To assess the robustness of the results based on sample size, a power analysis was performed. This analysis evaluated the power of the results by considering the number of effect sizes, the average number of participants per effect size, and heterogeneity. The power for two variables—overall survival of cancers and recurrence-free survival of cancers—could not be calculated because their results were reported in HR rather than SMD.

However, the power analysis revealed that all remaining variables were associated with high statistical power (Fig. 3 and Table 2). This finding indicates the adequacy of the sample size.

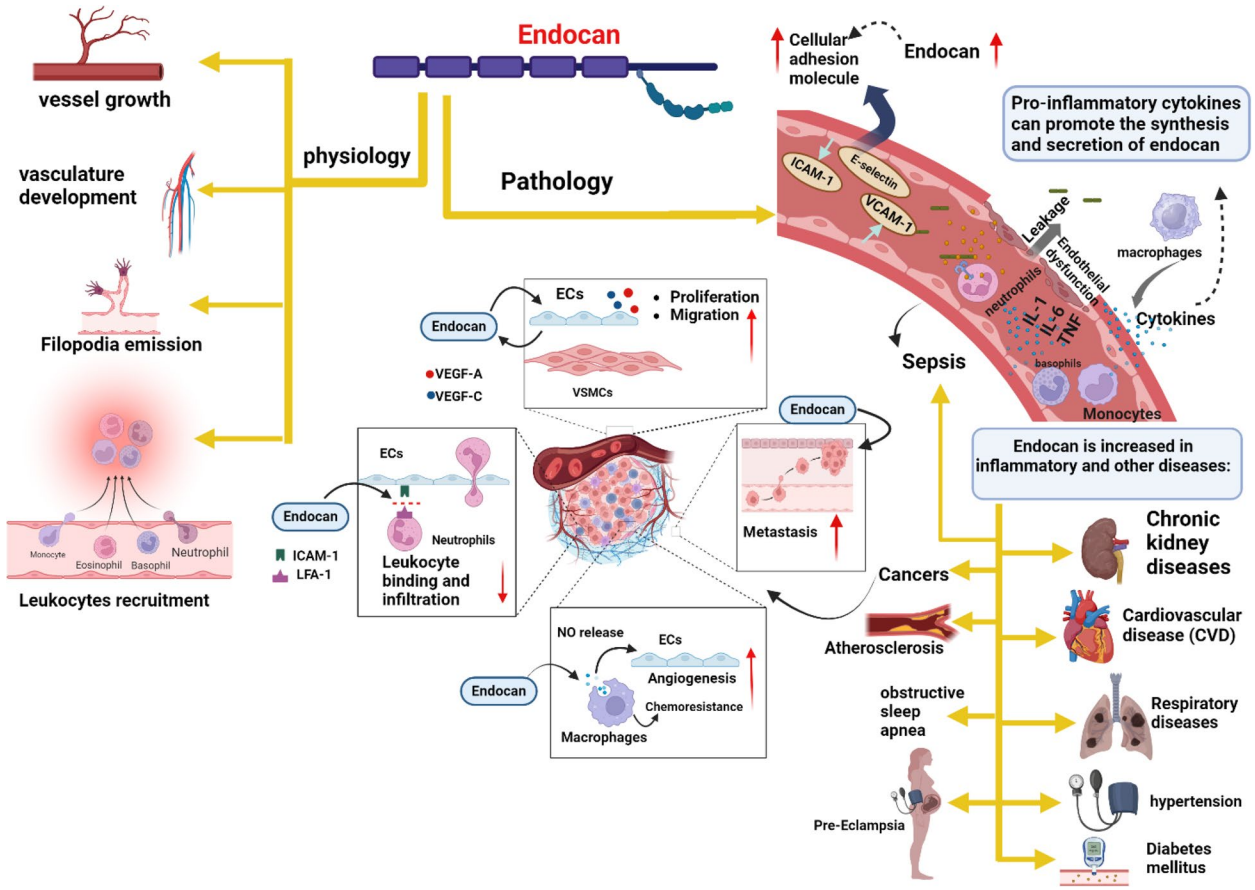


Fig. 4 The pathophysiology of endocan in different medical conditions

Results of GRADE assessment

According to the results of the GRADE assessment, the predictive value of endocan was rated as very low for preeclampsia, coronary artery disease, coronary slow flow, sepsis, multiple organ dysfunction syndrome, chronic kidney disease, COVID-19, and obstructive sleep apnea.

In contrast, it was rated as low for diabetes mellitus, recurrence-free survival of cancers, hypertension, sepsis mortality, and sepsis-related respiratory failure.

Additionally, the predictive value of endocan was classified as moderate for the overall survival of cancers (Table 3). Due to the low number of studies for acute respiratory distress syndrome (ARDS) and the inability to evaluate publication bias, we could not assess the GRADE for this outcome.

Discussion

In the current umbrella review, the aim was to assess the predictive value of endocan in various medical conditions and provide an overview of the current evidence by summarizing the results of previous meta-analyses. In summary, a total of 12 meta-analyses were identified, each contributing to the assessment of the predictive value of endocan across specific medical conditions, encompassing a total of 14 outcomes.

Endocan is a soluble proteoglycan that is primarily secreted by endothelial cells. When exposed to inflammatory markers such as interleukin (IL)−13 and tumor necrosis factor-alpha (TNF-α), its production rises. This increased expression results in increased levels of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), which in turn lead to increased leukocyte migration and inflammatory responses that are mediated by these cell adhesion molecules (Fig. 4) [5].

As the findings showed, patients with diabetes were found to have considerably greater levels of increased endocan in comparison to patients without diabetes. Importantly, this significant difference was observed in both diabetic patients with and without comorbidities.

Elevated levels of endocan in the bloodstream are perceived as a potential indicator of immuno-inflammatory

activity, reflecting endothelial activation and dysfunction often associated with diseases such as diabetes [9, 40] (Fig. 4). This connection between insulin resistance and endothelial dysfunction has been established through both experimental and clinical research, prompting the development of newer anti-diabetic medications aimed at addressing this link [41]. Given that the endothelium plays a critical role in the evolution of atherosclerotic events, which are one of the primary pathways via which diabetes affects health, endocan appears to be a promising predictive biomarker. Notably, endothelial dysfunction has also been linked to prediabetic disorders such as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which emphasizes the potential use of endocan in determining the likelihood and course of concerns related to diabetes [42–44].

The link between endocan and problems associated with diabetes has been validated by several research studies. In a study, Dallio et al. looked at endocan levels in patients with diabetes, non-alcoholic fatty liver disease (NAFLD), and people without the disease. They noticed that, in comparison to their non-diabetic counterparts, diabetic patients with NAFLD had noticeably higher levels of endocan [45]. Similarly, cirrhosis patients with diabetes showed noticeably greater levels of endocan than cirrhosis patients without diabetes in a study by Zuwala-Jagiello et al. [46]. Furthermore, Kose et al. discovered that patients presenting with acute coronary syndrome (ACS) and diabetes had considerably greater endocan levels than those without diabetes [47]. Moreover, Lv et al. found that those with diabetes and subclinical atherosclerosis had higher endocan concentrations than diabetic patients without this disease [48].

The current umbrella investigation revealed a significant connection between endocan and hypertension, a major risk factor for the development of additional cardiovascular events. In addition, the current umbrella study also showed a significant relationship between endocan and cardiovascular diseases like CAD and CSF. Additional research emphasized the part endocan plays in cardiovascular incidents. According to studies by Klisic et al., hypertension may rise by 32.2% for every 1 pg/mL increase in endocan levels [49]. A possible function for circulating endocan levels as a novel hypertension measure is suggested by the association between elevated endocan levels and increased arterial pulse wave velocity, which indicates arterial stiffness [19].

It is crucial to recognize that comorbidities in patients with cardiovascular diseases can influence their endocan levels. For instance, in our study, it was revealed that individuals with CAD who also had hypertension exhibited notably elevated blood endocan levels compared to those with hypertension alone. In another investigation by Wang et al., a comparison of endocan levels between hypertensive patients with CAD and those without CAD showed significantly higher serum endocan levels in the former group [50]. Similarly, Xiong et al. discovered higher serum endocan levels in patients with both hypertension and CAD in comparison to those with hypertension alone and without CAD[51]. Furthermore, de Souza and colleagues observed a positive correlation between endocan levels and systolic blood pressure in children who underwent renal transplantation. Specifically, individuals with both hypertension and CKD displayed significantly higher endocan levels than those with hypertension alone and without CKD [52].

A notable angiographic phenomenon is knownn as CSF is characterized by a delay in the opacification of coronary arteries even in the presence of an otherwisee normal angiogram appearance [53]. Serious cardiovascular problems are associated with this condition. Elevated serum endocan is related to CSF. It is involved in endothelial dysfunction, which is a major cause of CSF onset and progression [54, 55]. Significantly higher serum endocan levels were found in 93 patients as compared to controls, suggesting that endocan may be a useful biomarker for predicting the development and severity of CSF[56].

Endothelial dysfunction is closely associated with cardiovascular diseases such as high blood pressure, acute myocardial infarction, and CAD. Higher amounts of adhesion molecules and inflammatory chemicals coexist with varying degrees of endothelial dysfunction and vascular disorders as the condition worsens. Endocan expression promotes leukocyte adherence to endothelial cells and the circulation of inflammatory chemicals [9]. As a result, endocan has become known as an important marker of cardiovascular disease. As previously stated, endocan promotes the expression of molecules that are involved in cellular adhesion, such as E-selectin, VCAM-1, and ICAM-1. Leukocyte and endothelial cell migration is facilitated by ICAM-1, an essential adhesion protein that promotes cell adhesion responses and stabilizes cell contacts. It promotes the infiltration of inflammatory factors into the endothelium, stimulates endothelial cells, and fortifies the link between inflammatory cells and endothelial cells. Since vascular endothelial cells that are actively proliferating exhibit a higher level of ICAM-1 expression, angiogenesis may be triggered by leukocyte and endothelial cell adhesion mediated by ICAM-1 (Fig. 4). On the other hand, VCAM-1 facilitates the recruitment, adhesion, and migration of circulating monocytes to the arterial wall and binds specifically to mononuclear leukocytes and lymphocytes. It also plays a major role in the initiation of atherosclerosis [57]. It

is noteworthy that ICAM-1 levels are high during every stage of atherosclerosis, but VCAM-1 levels increase quickly and significantly after the onset of the atherosclerosis or during prominent inflammatory events as such vasospasm and plaque instability. Research shows that intermittent hypoxia significantly increases endocan expression through the HIF-1a/VEGF pathway, which in turn increases the expression of ICAM-1 and VCAM-1 and facilitates the adhesion of monocytes and endothelial cells [58] (Fig. 4).

The current umbrella review showed that the levels of endocan have significant importance in the prognosis of cancer. There was a strong relationship between higher levels of endocan and lower overall and recurrence-free survival in cancer patients. This correlation highlights the significant potential of endocan as a useful prognostic marker in the field of oncology.

Multiple studies have underscored the prognostic significance of endocan across various cancer types, including breast, prostate, lung, kidney, and liver cancer [59–65]. Moreover, some investigations have proposed endocan as a promising target for cancer therapy [63, 66]. In a previous study, 42 primary hepatocellular carcinoma (HCC) patients were analyzed. Tumor tissues and adjacent non-cancerous hepatic parenchyma were examined. After isolating endothelial cells, the researchers used immunohistochemistry, western blot analysis, reverse transcription-quantitative polymerase chain reaction, and immunohistochemistry to evaluate the expression of endocan. The findings showed that endothelial cells derived from HCC tumors significantly overexpressed endocan in comparison to liver tissues that were not cancerous [67].

The recent umbrella study's findings indicated a notable rise in serum endocan levels among individuals diagnosed with OSA, across all severity levels including mild, moderate, and severe cases. Furthermore, there was a correlation between serum endocan levels and various PSG indices and CIMT, thus implying a connection with OSA.

OSA is currently believed to be a low-grade chronic inflammatory illness, according to the literature [68, 69]. OSA is closely linked to the release of inflammatory cytokines by both endothelium and inflammatory cells [70, 71]. These factors result in inflammation and impact the functioning of endothelial cells [72]. In addition to the association with OSA, endocan is also connected to the development of lung inflammatory diseases that are mediated by immunological responses, such as acute respiratory distress syndrome, pneumonia, pulmonary thromboembolism, and COVID-19 [16, 73]. Elevated endocan levels are frequently seen in vascular disorders, which suggests the potential involvement of endovascular mechanisms in the pathogenesis of OSA. This is in addition to the role of endocan in inflammatory status. This connection is supported by research in the literature, which shows a link between endothelial dysfunction and OSA [73]. The increased risk of cardiovascular disease in those with OSA is partially explained by this connection [74]. OSA is linked to a number of comorbidities, such as stroke, cardiovascular disease, and cognitive decline, and it is known to cause systemic inflammation [75–77]. Recurrent episodes of upper airway damage related to sleep are thought to trigger systemic inflammation in OSA, ultimately resulting in vascular endothelial injury [78, 79].

Patients with CKD had elevated endocan levels, based on the current review. Inflammation and endothelial dysfunction play major roles in the etiology of CKD [7, 79–81]. Xu et al. conducted a cross-sectional study in which 80 patients with hyperuricemic nephropathy at different stages of CKD had their plasma endocan levels compared. The results showed that individuals in stages 3–4 of CKD had higher levels of endocan than patients in stages 1–2 [82]. Along similar lines, further research has shown higher endocan concentrations in hemodialysis patients in comparison to those with end-stage CKD and healthy individuals [83]. These findings indicate a potential relationship between endocan levels and the progression of CKD stages by highlighting the correlation between higher endocan levels and advanced stages of CKD. Another study by Oka et al. discovered a positive correlation between baseline peripheral endocan concentration, serum creatinine, and serum TNF-α [84]. Furthermore, patients with proteinuria and elevated endocan levels experienced a sharp decline in urine volume. Endocan levels may rise as a result of mediators like TNF-α and interleukin-1 beta (IL-1β) inducing endothelial damage due to toxins in the bloodstream of patients with CKD [85–87].

Through this thorough investigation, we showed an established connection between elevated endocan levels and mortality due to sepsis, in addition to its association with multiple organ dysfunction syndrome and respiratory distress associated with sepsis. Additionally, earlier research has shown the importance of endocan as a predictor of bacteremia, the requirement for vasopressor assistance, and the onset of respiratory failure [66, 88–90]. This suggests that endocan has the potential as a useful predictive biomarker that can anticipate when challenges for septic patients can arise. Compared to the Lung Injury Prediction Score (LIPS), high endocan levels have been found to be a more reliable predictive biomarker for acute respiratory distress syndrome (ARDS), a higher area under the curve [38, 91]. Furthermore, there is a correlation between higher endocan levels and higher requirements for mechanical ventilation [92]. Previous studies have demonstrated the association between

acute systemic inflammation and endocan levels, which increases the risk of multiple organ failure and respiratory compromise in septic patients [14, 91–95] (Fig. 4).

According to the findings from the present umbrella review, women diagnosed with preeclampsia exhibit elevated circulating levels of endocan in comparison to those with uncomplicated pregnancies. Additionally, the mean maternal age appears to play a potentially significant role in influencing these outcomes. Notably, it was shown a statistically significant increase in circulating endocan among women experiencing late-onset preeclampsia in contrast to those with normal pregnancies. However, this disparity lost statistical significance when comparing early-onset preeclampsia with normal controls.

While the results of this umbrella review highlight the statistical significance of endocan as a biomarker in predicting disease progression, its potential clinical integration is an important next step. Endocan, due to its role in endothelial dysfunction and inflammation, could be particularly useful in the early detection of cardiovascular diseases, chronic kidney disease, and diabetes. For instance, endocan levels could be measured as part of routine screening protocols for patients at high risk for these conditions, such as those with hypertension, diabetes, or a family history of cardiovascular diseases. By incorporating endocan testing into clinical workflows, healthcare providers could gain valuable insights into endothelial health, enabling earlier interventions aimed at preventing the progression of vascular complications.

In more acute settings, such as sepsis or acute respiratory distress syndrome, endocan could be utilized as a prognostic marker to assess the severity of disease and predict patient outcomes. Given its association with mortality and organ dysfunction in sepsis, measuring endocan levels upon admission could help prioritize patients for intensive monitoring or more aggressive interventions, particularly in resource-limited settings. Furthermore, its role in COVID-19 prognosis suggests that endocan could be integrated into the management of infectious diseases, offering clinicians an additional tool to gauge patient risk and tailor treatment approaches more effectively.

To facilitate the clinical translation of Endocan as a reliable biomarker, several important directions for future research must be addressed. First, the standardization of measurement methods is essential. Endocan can be measured using various assay types and in different biological specimens (e.g., plasma or serum), which may lead to inconsistent results. Therefore, future studies should clearly report the measurement methods used and consider performing subgroup analyses based on assay type and specimen source to identify potential sources of heterogeneity.

Additionally, diagnostic meta-analyses should be conducted to evaluate Endocan's diagnostic performance in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. Alongside this, the determination of standardized cut-off values is crucial, including well-defined normal and abnormal reference ranges. This will support the clinical interpretation of Endocan levels and allow for consistent use in patient care.

There is also a need to explore Endocan's role in a broader range of diseases, as current research has primarily focused on a limited number of clinical conditions. Evaluating its diagnostic and prognostic utility across various disease states—including inflammatory, cardiovascular, infectious, and oncologic disorders—could significantly expand its relevance in medicine.

Importantly, large-scale prospective studies are required to validate the clinical usefulness of Endocan. These studies should aim to confirm its predictive value in real-world settings and help define its position in clinical algorithms. Furthermore, the cost-effectiveness of incorporating Endocan testing into routine clinical practice should be assessed, particularly in comparison with existing biomarkers or standard clinical tools. This would ensure that its adoption provides tangible benefits in terms of healthcare resource allocation.

Finally, aspects such as the feasibility and accessibility of endocan measurement in different healthcare environments should also be evaluated. These practical considerations, along with the development of expert guidelines and consensus recommendations, will be key in shaping how and where endocan is used in clinical practice.

Advantages, limitations, and future suggestions

To the best of our understanding, this current review represents the first umbrella study aimed at evaluating and consolidating the predictive significance of endocan across various medical conditions, synthesizing findings from previous meta-analyses in this domain. Moreover, we evaluated the meta-analyses' quality and performed power analyses to ascertain the robustness of the results. Additionally, we conducted a GRADE assessment to estimate the epidemiological strength of the outcomes.

However, the current evidence is accompanied by several limitations that warrant attention in future studies. A major concern is the overall low methodological quality of the included meta-analyses, as rated by AMSTAR2. In most cases, these issues stemmed from unjustified

heterogeneity and the absence of pre-registered protocols. This highlights the critical need for future meta-analyses to adhere to rigorous methodological standards. Specifically, upcoming studies should aim to use larger sample sizes to enhance statistical power and reduce imprecision. Additionally, researchers should pre-register their protocols (e.g., in PROSPERO) and clearly report any deviations from the original plan to ensure transparency and reproducibility.

Another limitation was that many of the outcomes exhibited moderate or high heterogeneity, diminishing the epidemiological robustness of the findings. We strongly recommend that future meta-analyses undertake various subgroup and meta-regression analyses to identify the sources of this heterogeneity.

Additionally, the assessment of publication bias posed limitations. Although we reported the results of publication bias using Begg's and Egger's tests where available, some meta-analyses included only one of these tests, and in some cases, the number of primary studies was fewer than ten. As a result, the statistical power of publication bias assessments was limited. To enable a more accurate and statistically meaningful assessment of publication bias in future reviews, more original studies are needed, particularly in disease areas where the current body of evidence is sparse.

While the association between endocan and various diseases is documented, a key limitation is that most of the included studies were cross-sectional in nature and did not assess causality. As a result, it remains unclear whether elevated endocan levels are a consequence of disease progression or severity or whether they may actively contribute to disease development and worsening. To address this gap, there is a pressing need for longitudinal studies that can explore the temporal relationship between elevated endocan levels and disease outcomes. Such studies would provide more definitive evidence regarding the causal role of endocan, helping to determine whether it is merely a biomarker of existing pathology or a predictive factor influencing disease trajectory.

Another limitation was insufficient reporting on the methods used for endocan measurement across studies. Given that endocan can be measured using various techniques and in different biological specimens (e.g., plasma or serum), this variability may introduce measurement bias and contribute to between-study heterogeneity. Unfortunately, due to the lack of detailed data, we were unable to assess or stratify the findings based on the measurement method. Future studies should aim to clearly report the methods used for endocan measurement, including the type of assay, specimen source (e.g., plasma or serum), and any relevant procedural details. Accurate and transparent reporting will allow for better comparability across studies and facilitate more reliable evidence synthesis. Additionally, researchers are encouraged to perform subgroup analyses based on measurement methods or specimen types. This would help to identify potential sources of heterogeneity and assess whether differences in methodology significantly influence study outcomes.

While we identified 12 meta-analyses for inclusion in the current umbrella review, multiple original studies investigating the predictive value of endocan in conditions such as nonalcoholic fatty liver disease, metabolic syndrome, rheumatoid arthritis, malignancy, systemic lupus erythematosus, heart failure, and other diseases are available [96–101]. There is a need for additional meta-analyses on these diseases to expand our understanding of the predictive utility of endocan. Such efforts would significantly contribute to advancing our knowledge in this area.

Conclusion

Endocan has emerged as a promising and innovative biomarker, demonstrating its potential in a range of health conditions. It is relevant to critical areas such as COVID-19, chronic kidney disease, obstructive sleep apnea, diabetes mellitus, coronary artery disease, and preeclampsia. This versatile applicability underscores the importance of endocan in advancing our understanding and diagnostic capabilities. Further studies are necessary to evaluate endocan's specificity, sensitivity, and clinical applicability. Clinically, endocan could be integrated into routine screenings, particularly for at-risk populations, to facilitate early detection and more targeted interventions. By monitoring endocan levels, healthcare providers could enhance their ability to predict disease progression, optimize treatment strategies, and ultimately improve patient outcomes.

Abbreviations

AMSTAR 2	A measurement tool to assess systematic reviews, version 2
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CMA	Comprehensive meta-analysis
COVID-19	Coronavirus disease 2019
CSF	Coronary slow flow
FMD	Flow-mediated dilation
GRADE	Grading of recommendations, assessment, development, and evaluation
HR	Hazard ratio
ICAM-1	Intercellular adhesion molecule 1
SMD	Standardized mean difference
NCF	Normal coronary flow
OSA	Obstructive sleep apnea
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
TNF-α	Tumor necrosis factor-alpha
VCAM-1	Vascular cell adhesion molecule-1

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
The research idea was offered by S.S.N, N.T, and E.AS. The proposed search was carried out by S.H., N.T, and E.AS. The illustrations were designed by S.N and E.AS. N.T, S.S.N, M.H.K. and S.N. looked through the databases. The included studies were appraised by S.S.N, R.N., E.AS, and D.A. The manuscript was drafted in collaboration with all authors.

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Data availability
The datasets used and/or analyzed during the current study can be provided by the corresponding author upon reasonable request.

Declarations

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Competing interests
The authors declare that they have no competing interests.

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