REVIEW

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# Artificial intelligence in the management of chronic venous insufficiency: a systematic review

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## ABSTRACT

**Introduction:** Chronic venous insufficiency (CVI) is a prevalent condition with significant health and economic burdens. As the condition progresses, it can severely impact patients' quality of life. Recent developments in Artificial Intelligence (AI) in healthcare offer promising solutions, providing tools that can enhance the accuracy of diagnosis, improve disease staging, and guide treatment decisions. This study aims to comprehensively synthesize and evaluate the role of AI techniques applicable to the management of CVI based on current evidence.

**Methods:** Adhering to 2020 PRISMA guidelines, we systematically searched Pubmed, Science Direct, CENTRAL, and Scopus for studies published in 2014–2024 which applied AI techniques in the management of CVI. We excluded studies that were case reports, case series, review articles, guidelines, or those that contained unpublished or incomplete data, or where the full text was not available in English or Indonesian. Analyses used descriptive statistics to summarize findings, emphasizing the reported statistical results. Risk-of-bias was assessed using the Prediction model Risk Of Bias Assessment Tool (PROBAST).

**Results:** Our review of 9 studies found that AI, including deep learning and machine learning, achieved moderate to high accuracy or performance in CVI management, including diagnosis and prognosis. AI techniques employed include deep convolutional neural networks, natural language processing, computer vision, fuzzy logic, logistic regression, and random forest. CVI severity, ulcer size and etiologies, as well as the risk of ulcer development could be predicted by the AI. The majority of the studies (88,9%) demonstrated a high or unclear risk of bias. AI has demonstrated significant potential in enhancing the management of CVI patients, particularly in diagnosis, prognosis, and decision-making support.

**Conclusion:** AI has shown significant potential in enhancing the management of CVI patients, particularly in diagnosis, prognosis, and decision-making support. However, further high-quality quantitative studies are needed to confirm its effectiveness.

**Keywords:** Artificial Intelligence, Chronic venous insufficiency, Disease Management.

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## INTRODUCTION

Chronic venous insufficiency (CVI) is a prevalent condition with high burden. CVI is characterized by impairment of superficial or deep venous blood flow causing venous hypertension and a number of pathological changes, such as lower extremity edema, skin trophic changes, and discomfort. The basic etiopathophysiology is thought to be involving valvular reflux, venous outflow obstruction, arteriovenous malformation, calf muscle pump disturbance, and hereditary diseases.[1] It is also associated with arterial hypertension, venous thrombo-embolism, and peripheral artery disease.[2]

There are approximately 150,000 new cases of CVI every year.[1] Epidemiological Study of the Vein Consult Program showed the prevalence of CVI was 19,84% in Asian region.[3] One study in Singapore showed venous leg ulcers have substantial economic burden on healthcare. Inpatient bill was S$7886 for an average patient, where the outpatient bill was S$6962.[4] One study in the United States also showed higher total cost in inpatient bill than outpatient bill, with average per patient $33,629 vs $10,851.[5]

If neglected, CVI becomes progressive, contributing to serious disturbances of life quality and productivity, especially in patients with apparent risk factors, hence prolonged treatments and hospital length of stay. Therefore, CVI holistic management starting from immediate and accurate recognition, screening, diagnosis, and treatment are required.[1,6] Nowadays, with technology evolving at rapid pace, such management can be assisted by several innovations in form of Artificial Intelligence (AI) capable of assessing CVI diagnosis, staging, classification, and even treatment decisions. AI connects the gap between big data, clinical providers, and new technology. This impact of AI in thorough CVI management is expected to be beneficial.[7] With the increased CVI prevalence and burden, especially due to delayed and incorrect management, as well as advancement of AI technologies in healthcare, this study aims to comprehensively synthesize and evaluate the role of AI techniques applicable to the management of CVI based on current evidence. This study aims to comprehensively synthesize and evaluate the role of AI techniques applicable to the management of CVI based on current evidence.

## METHODS

This systematic review adhered to 2020 Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines. In the PROSPERO International Prospective Register of Systematic Reviews, the review was not registered.

### Search Strategy and Eligibility Criteria

A comprehensive search strategy was developed to identify articles reporting AI techniques in the management of CVI. A thorough search was conducted on electronic databases including Pubmed, Science Direct, CENTRAL, and Scopus in July 2024. Manual searches of bibliographies, citations, and related articles of included studies were performed. Research articles were searched with keywords and Medical Subject Headings (MeSH) terms for CVI and AI.

Original research studies published within the last ten years (2014–2024) were included if they met the inclusion criteria, as the rapid growth and development of AI research in this period is particularly relevant to the focus of this review. The inclusion criteria were primary research articles which used AI techniques in CVI management, including the screening, diagnosis, treatment, and/or prognosis. CVI was defined as a condition characterized by impairment of superficial or deep venous blood flow causing venous hypertension and a number of pathological changes, such as lower extremity edema, skin trophic changes, and discomfort. AI was defined as a computational program able to perform tasks that are characteristics of human intelligence, such as image and pattern identification, recognition, analysis, learning from past experience, problem solving, and decision-making, including–but not limited to–the subtypes of machine learning and deep learning, such as random forest and fuzzy logic. Manuscripts were excluded if they were case report, case series, review article, guideline, contained unpublished or incomplete data, or the full text was not available in English and/or Indonesian.

### Study Selection

Titles and abstracts were independently screened by all three authors (AR, YBSS, KWAP). Full texts meeting the inclusion criteria were reviewed by all authors, with discrepancies discussed and resolved to reach a consensus on eligibility.

### Data Extraction and Analysis

Data extraction was performed in the included studies using a previously determined data extraction form consisting of study title, published year, data source, AI types and algorithms, study objective, and outcomes. The studies are presented by separated tables based on the category of the AI use (screening and diagnosis, prediction, treatment, or others/unspecified utility). The results are described narratively. Analyses were performed using descriptive statistics of the data and summarized the findings from these studies, with emphasis on statistical results reported in each study. Quantitative synthesis was not carried out due to limited number of the studies and their heterogeneity.

### Risk-of-Bias Assessment

The included studies were assessed for its eligibility and risk of bias using the Prediction model Risk Of Bias Assessment Tool (PROBAST).[8] PROBAST contains 3 steps of assessment starting with 4 domains and the signaling questions, a risk of bias determination step, and applicability judgment. The signaling questions are related to the studies participants, predictors, outcomes, and analyses. The applicability is assessed from the suitability of participants or the setting, the predictors, or the outcomes with the review question.

## RESULTS

### Study Selection

Figure 1 shows a PRISMA flow chart depicting the study selection process.

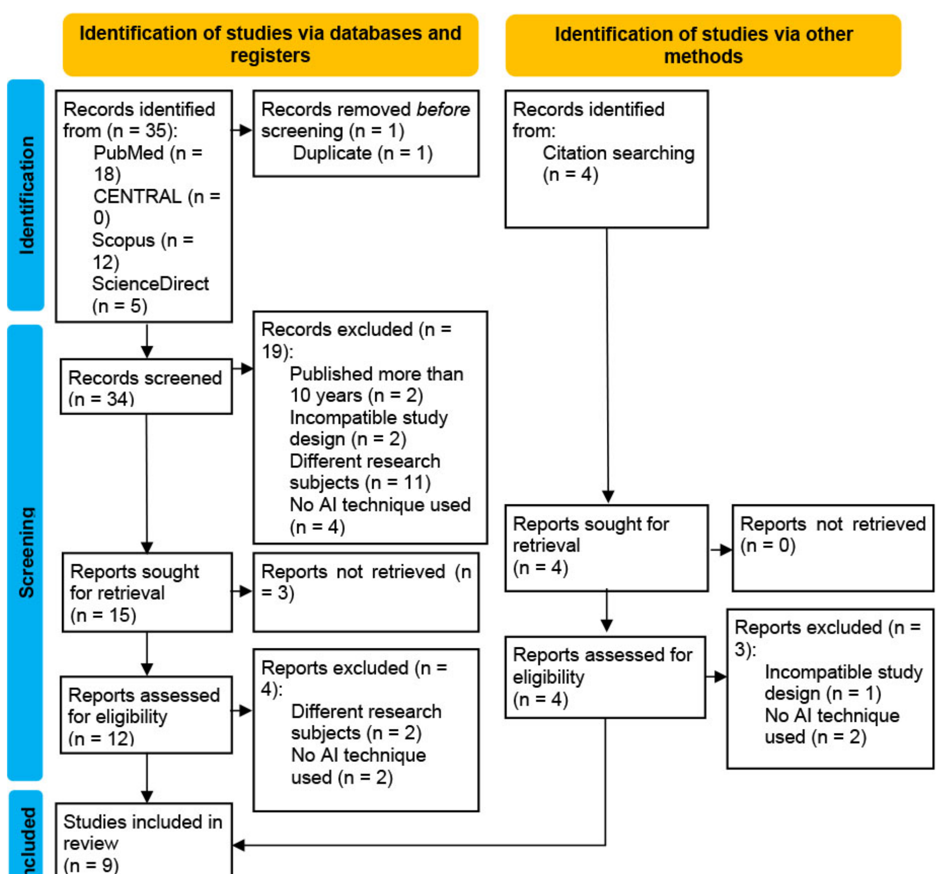


**Figure 1.** Literature selection process.

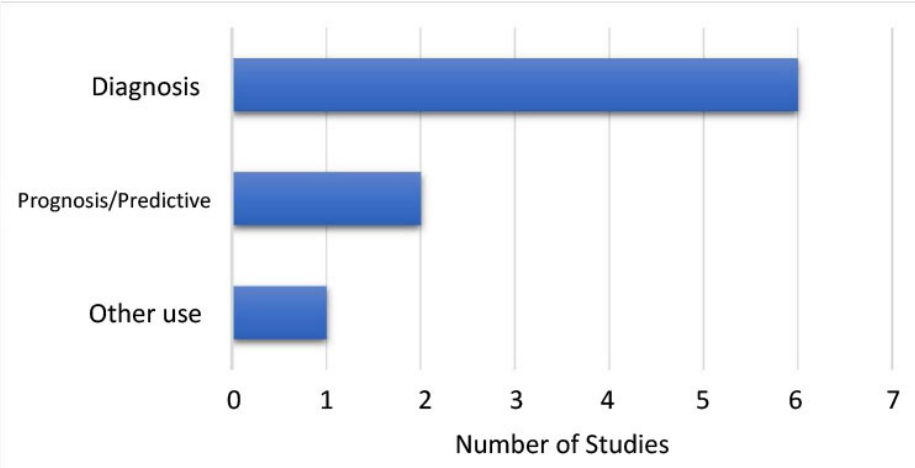


**Figure 2.** AI application in the included studies.

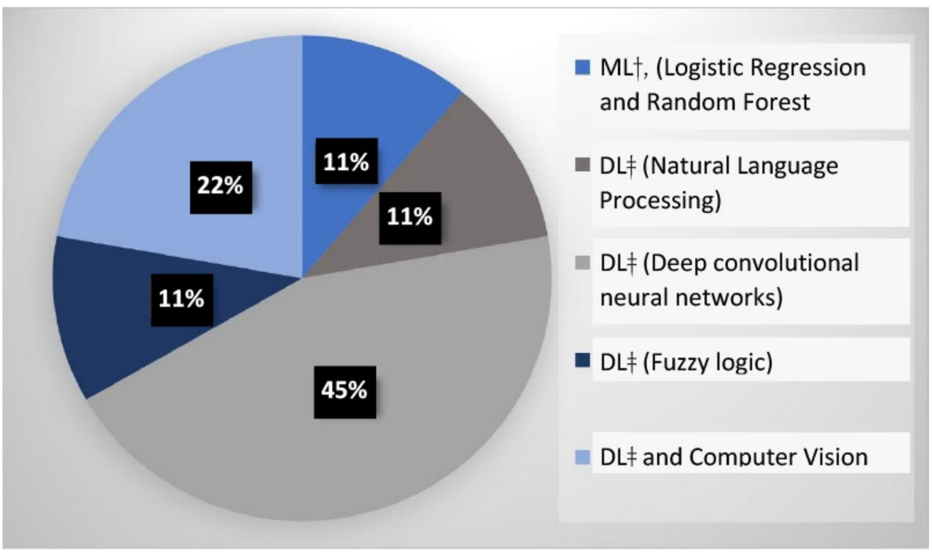


**Figure 3.** AI algorithm used in the studies. Note: †machine learning, ‡deep learning.

Four online databases and citation searching yielded a total of 39 studies. After duplicates removal, at the initial screening, there were 19 studies excluded due to either incompatible study designs, not including CVI management, not using AI techniques, or published more than 10 years ago. Three studies were not retrieved since the full-text papers were not available. After reviewing the potentially eligible studies, 6 studies were excluded due to either different research subjects, incompatible study design, or not including AI techniques. Finally, we included 9 final studies to be reviewed.

## Study Characteristics

This review included 9 original research papers published between 2015–2024.[9–17] Four studies included data inputs which consist of human patients,[10–13] while others used electronic data (datasets, clinical images, medical records, questionnaires).[9,14–17] These studies utilized various types of AI algorithms, such as deep convolutional neural networks (DCNN), natural language processing, computer vision, fuzzy logic, logistic regression, and random forest classifier. Total of 7 studies assessed the performance of AI tools (in terms of accuracy, precision, recall, or area under the curve (AUC)),[9,11,13–17] while only 2 studies conducted clinical validation of the AI techniques.[10,12] Six studies examined the use of AI in CVI screening and diagnosis,[10–12,15–17] 2 studies assessed AI use in predicting CVI outcomes,[13,14] while 1 study assessed unspecified AI use in CVI, which referred to AI general benefits on CVI management in healthcare.[9] Figure 2 and 3 show the AI application and AI algorithm used in the included studies.

## AI Techniques in CVI Management

### As Screening and Diagnostic Tools

Six studies examined AI use in diagnosing CVI.[10–12,15–17] The diagnostic features of the AI varied from detecting CVI severity based on clinical images, differentiating venous ulcers from other leg ulcers etiologies, to measuring the size of venous ulcers. Studies involving DCNN generally showed DCNN precision of 0.58–0.93, recall of 0.6–0.92, and accuracy of 0.61–0.93. Based on segmenting and severity classifying ability, DCNN showed better accuracy, precision, recall, and F1-score in classifying CVI severity with value of >95% for each parameter. Compared to other existing classification DCNN, the average values of all parameters above were higher. However, in segmenting CVI images, DCNN tends to have moderate DICE coefficient, precision, and recall (around 60–80%) in segmenting telangiectasia veins, varicose veins, and all types of venous lesions, with the best precision and recall in venous ulcers segmentation (>90%).

In addition, DCNN detected venous leg ulcers better through cropped images, with sensitivity, specificity, accuracy, and F1 score higher than through full images.[15] In detecting ulcer type, as much as 53% venous ulcers were able to be assigned correctly by DCNN. DCNN could also determine predilection of venous leg ulcer, showing dorsal medial leg part as the most common area for venous ulcer emergence.[11]

On the other hand, DL and computer vision had significant intra- and inter-rater reliability in measuring venous leg ulcers size (length, width, and area), with score of >0.95 for each dimension aspect both in intra- and inter-rater reliability analyses. Compared to measurement performed by trained wound nurses, the devices also had significant inter-rater reliability in terms of length, width, and area with scores of 0.75-0.93, separately and overall.

### As Prognostic Tools

Two studies examined the use of AI in predicting CVI and/or its complications.[13,14] In a study by de

**Table 1. Summary of the included studies**

| Author | Year | AI* Application | AI* Tool | Data Source | AI* Prediction Output | Study Objective | Outcomes |
|---|---|---|---|---|---|---|---|
| Athavale, et al | 2023 | Other use | DL† (Natural Language Processing) | - Non-complex questions (medical and administrave)<br>- Complex medical questions requiring expertise in CVD‡ | Assessment of ChatGPT performance in providing informative answers on medical related questions. | To assess whether chatbots could assist with answering patient questions and electronic health record inbox management. | On non-complex medical questions: ChatGPT 4.0 = grade 1 on 20 of 20 questions (100%). ChatGPT 3.5 = grade of 1 on 14 of 20 (70%), grade 2 on 4 of 16 (20%), grade 3 on 0 (0%), grade 4 on 2/20 (10%) questions.<br><br>On complex medical questions:<br>-ChatGPT 4.0 = grade 1 on 15 of 20 (75%), grade 2 on 2 of 20 (10%), grade 3 on 2 of 20 (10%), grade 4 on 1 of 20 (5%) questions.<br>-ChatGPT 3.5 = grade 1 on 9 of 20 (45%), grade 2 on 4 of 20 (20%), grade 3 on 4 of 20 (20%), grade 4 on 3 of 20 (15%) questions.<br>-Clinical Camel = grade 1 on 0 of 20 (0%), grade 2 on 5 of 20 (25%), grade 3 on 5 of 20 (25%), grade 4 on 10 of 20 (50%) questions |
| Chan, et al | 2022 | Diagnosis | DL† and computer vision | 52 patients with VLU§ | Detection of VLU§ dimension size | To compare intra- and inter-rater reliability of a ML‖-based handheld 3-dimensional infrared wound imaging device (WoundAide [WA] imaging system, Konica Minolta Inc, Tokyo, Japan) to traditional measurements by trained wound nurse. | -Intra-rater reliability ($P < 0.001$): length (0.978-0.989), width (0.978-0.980), area (0.990-0.992).<br>-Inter-rater reliability between the three WA devices ($P < 0.001$): length (0.983-0.990), width (0.988-0.992), area (0.994-0.996).<br>-Inter-rater reliability between each of 3 devices and trained wound nurse ($P < 0.001$): length (0.875-0.889), width (0.891-0.900), area (0.932-0.950). |

| Author | Year | AI[*] Application | AI[*] Tool | Data Source | AI[*] Prediction Output | Study Objective | Outcomes |
|---|---|---|---|---|---|---|---|
| Deinsberger, et al | 2022 | Diagnosis | DL[†] (Deep convolutional neural networks) | 277 patients presenting altogether with 717 lower leg ulcers | Detection of leg ulcers etiology | To provide a comprehensive analysis of predilection sites of various types of lower leg ulcers and evaluated ulcer location | Overall cases: Prec[¶]: 0,58; Rec[#]: 0,6; Acc[**]: 0,61 Acc[**] after the 5-fold cross-validation: 0.68<br><br>Venous leg ulcers detection performance: -53% assigned correctly; 27% misdiagnosed as mixed arterial and venous ulcer; 13% misdiagnosed as vasculitis; 6,7% misdiagnosed as Arteriolosclerotic ulcer of Martorell<br><br>Venous leg ulcer predilection: The most frequent localization: DM2[††] 36.7% (114), VM2[‡‡] (24.8%, 77), VM1[‡‡] (22.6%, 70), VL1[$$] (21.0%, 65). |
| Fong, et al | 2022 | Diagnosis | DL[†] and computer vision | 82 Asian VLU[$] patients with a total of 358 wound episodes and 2334 wound images | Measurement of ulcer length, width, and area | To clinically validate the accuracy of a smartphone wound application (TA[\|\|\|\|]), versus conventional wound measurements (visual approximation and paper rulers), in patients with VLU[$] | Inter-rater and Intra-rater reliability for ulcer length, width and area Inter-rater reliability (P < 0.001): -Between the measurements made by the wound nurse and with the TA[\|\|\|\|] running on both iOS and Android devices (0.799-0.919 for iOS; 0.803-0.914 for Android) -Between TA[\|\|\|\|] running on the iOS versus Android (0.987-0.989)<br><br>Intra-rater reliability (P < 0.001): -Between 3 different images of the same wound taken by the same iOS or Android device running TA[\|\|\|\|] (0.967-0.985 for iOS and 0.977-0.984 for Android) |
| Franciscis, et al | 2015 | Prognosis/ Predictive | DL[†] (Fuzzy logic) | CVD‡ patients with CVU[###] (C5–C6 of CEAP classification) and a control group (CVD‡ patients without CVUs[###] (C1–C4 of CEAP classification)) | Prediction of CVU[###] development in CVD‡ patients | To identify the stratification risk of patients with CVD‡ developing CVU[###] | Score < 18%: a low risk. Score > 18%: the possibility of developing ulcers. Score >22%: the start of the high risk area. |

| Author | Year | AI* Application | AI* Tool | Data Source | AI* Prediction Output | Study Objective | Outcomes |
|---|---|---|---|---|---|---|---|
| Han, et al | 2024 | Prognosis/ Predictive | ML[‖] (Logistic Regression and Random Forest Classifier) | 100 samples and 43 features related to CVI*** from previous study[18] | Prediction of CVI*** classification (VCSS [†††]) before, after 1 month, and after 3 month of yoga practices | To assess performance of ML[‖] models with different optimization strategy on predicting CVI*** classification (VCSS[†††]) based on selected features before, after 1 month, and after 3 month of yoga practices | RFGT [‡‡‡] model's AUC**** score:<br>- VCSS[†††]-Pre in Absent, Mild, Moderate, Severe: 0.9072, 0.8714, 0.7709, 0.7200<br>- VCSS[†††]-1 Month in Absent, Mild, Moderate, Severe: 0.9158, 0.8644, 0.8142, 0.6333<br>- VCSS[†††]-3 month in Absent, Mild, Moderate, Severe: 0.9269, 0.8399, 0.7838, 0.7500 |
| Malihi, et al | 2022 | Diagnosis | DL[†] (Deep convolutional neural networks) | 909 wound images from two wound care centres and openly available wound images | Detection of leg ulcers type | To classify venous leg ulcers and diabetic foot using wound images | For venous leg ulcer detection:<br>On cropped images: Sn[++++] 94%, Sp[‡‡‡‡] 75%, Acc** 83%, F1-score 0,85<br>On full images: Sn[++++] 65%, Sp[‡‡‡‡] 70%, Acc** 67%, F-1 Score 0,7 |
| Oliveira, et al | 2022 | Diagnosis | DL[†] (Deep convolutional neural networks) | 1376 photographs of patients with CVD‡ in lower limbs, database was constructed from normal clinical practice, where 502 images were collected from two public datasets | Detection of CVI*** severity | To classify CVD‡ severity from medical images | Acc** 93,8%, Prec[¶]: 93,4%, Rec[#]: 92.4% |
| Oliveira, et al | 2023 | Diagnosis | DL[†] (Deep convolutional neural networks) | Dataset of 1376 CVD‡ images. | Detection of CVI*** segmentation and severity classification | To segment CVD‡ and classify its severity from medical images. | "Ablation Studies" Performance:<br>-Segmentation: 78.3% DICE, Acc**: 81.7%, Rec[#]: 77.6%.<br>-Classifcation: Acc** 97.8%, Prec[¶] 97.6%, Rec[#] 98.5%, F1-score 97.8%. |

Note: *Artificial Intelligence; †Deep learning; ‡Chronic Venous Disorder; [§]Venous Leg Ulcer; [‖] Machine learning; ¶Precision; #Recall; **Accuracy; [††]Dorsal Medial; [‡‡]Ventral Medial; [§§]Ventral Lateral; [‖‖] Tissue Analytics; [###]Chronic Venous Ulcer; [¶¶]Clinical, Etiological, Anatomical, and Pathophysiological; ***Chronic Venous Insufficiency; [‡‡‡]Random Forest Classifier with Giant Trevally Optimizer; ****Area under the curve; [†††]Venous Clinical Severity Score; [++++]Sensitivity; [‡‡‡‡]Specificity

Franciscis et al, an AI based on fuzzy logic was used to determine the stratification risk of CVI patients developing venous ulcers, resulting in risk scores (low, possible, high) allowing easier process of predicting a CVI complication based on patient's multiple comorbidities.[13] Another study assessing logistic regression and random forest classifier showed the best AUC score in predicting CVI classification (VCSS) absent groups, with a score of >0.90 and the highest in 3 months after yoga practices.[14]

### Other Use

Study by Athavale et al which examined natural language processing in forms of ChatGPT 4.0 versus ChatGPT 3.5 versus Clinical Camel performances in CVI management decision making reported that ChatGPT 4.0 provided better and more reliable answers hence the more accurate guidance in assisting healthcare providers, also allowing medical information retrieval in medical education generally.[9]

### Risk-of-bias Assessment

Figure 4 and Table 2 summarized the risk-of-bias assessment using PROBAST. Of the 9 included studies, overall risk of bias was high for 4 (44,4%) studies, unclear for 3 (33,3%) studies, and low for 1 (11,1%) study. In analysis domain, there was a lack of information regarding timely and accurate description of model metrics, missing data handling, and/or unclear assessment of overfitting correction and adaptation. In outcome domain, some studies did not determine the outcome without knowledge of predictor information and had lack of information in standard outcome definition used, leading to high risk of bias. In participant domain, patient selection was often not clearly declared, nor was there a clear description of inclusion and exclusion criteria. This leads to high and/or unclear concern in applicability in 88.9% studies.

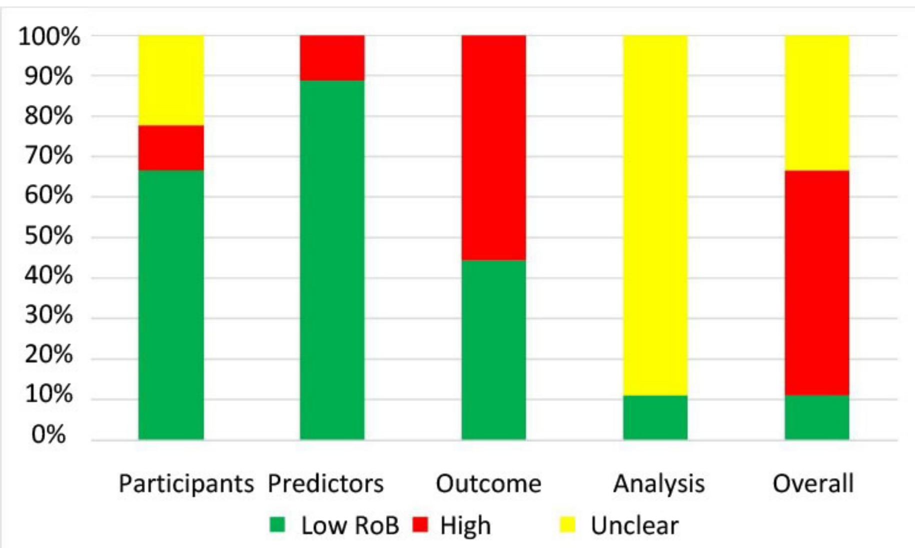


**Figure 4.** Risk-of-bias assessment of included studies using Prediction Model Risk of Bias Assessment Tool (PROBAST).

## DISCUSSION

This study demonstrated a comprehensive synthesis of current evidence in AI use in the CVI management. AI, in the form of deep learning and machine learning, and their subsets has shown to be a helpful advancement in patient management, including diagnosis, prognosis, and decision making support.

Most diagnostic studies utilized the DL technique. DL begins with data collection (e.g. datasets of CVI-related images), followed by preprocessing to enhance features and reduce noise, feature extraction, labeling, and model selection. DL can analyze medical images to identify signs of CVI, predict its progression, highlight key patterns, integrate multiple data sources, and suggest optimal treatments based on clinical picture. The most common model used for image

**Table 2. Risk-of-bias assessment of included studies using Prediction Model Risk of Bias Assessment Tool (PROBAST)**

| Author, Year | Risk of Bias | | | | Applicability | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|
| | 1.Participants | 2.Predictors | 3.Outcome | 4.Analysis | 1.Participants | 2.Predictors | 3.Outcome | Risk of Bias | Applicability |
| Athavale et al, 2023 | - | + | - | ? | - | + | - | - | - |
| Chan et al, 2022 | + | + | - | ? | + | + | - | - | - |
| Deinsberger et al, 2022 | + | - | - | ? | + | + | ? | - | ? |
| Fong et al, 2022 | + | + | + | + | ? | + | + | + | ? |
| Franciscis et al, 2015 | + | + | - | ? | + | + | - | - | - |
| Han et al, 2024 | ? | + | + | ? | ? | + | + | ? | ? |
| Malihi et al, 2022 | + | + | + | ? | + | + | + | ? | + |
| Oliveira et al, 2022 | ? | + | + | ? | ? | + | + | ? | ? |
| Oliveira et al, 2023 | + | + | - | ? | + | + | - | - | - |

related tasks is Convolution Neural Network (CNN),[18] similar to the findings in this review.

DCNN had moderate-to-high accuracy, precision, recall, and classification ability in detecting CVI through the lesion images. This is in line with existing studies. DCNN has been reported to have promising results in predicting, classifying, and analyzing medical pictures, proven by its high accuracy, precision, recall, Kappa, and F1-score values, due to its deep learning capability to capture complicated patterns in data including complex cardiovascular related data, such as CVI.[19,20] DCNN also has good metrics especially in classification tasks and images.[20] Those studies suggested DCNN had better performance compared to other algorithms, such as ML.[20–22] Nevertheless, other study proposed neural networks showed the best performance in CVI classification, but only with fairly good accuracy.[23] However, in DL or DCNN use, inappropriate or biased datasets can exaggerate existing biases in predictions and insignificant model performance.[20]

Computer vision is able to calculate the size, identify the contours, and categorize wounds tissues, including their evolution over time.[24] Result in our study showed high intra- and inter-rater reliability computer vision and trained wound nurses. This finding aligns with study by Reifs et al,[24] which also reported high visual computing methods inter-rater reliability score in detecting wound contour. Another review and meta-analysis found that diagnostic performance DL models were comparable to that of healthcare providers. This was evidenced by similar pooled sensitivity and specificity values, demonstrating excellent result consistency.[25] The challenge in computer vision application has to do with the wound surface. If not completely captured by the lens, the area measurement will only be partially valid and require additional photos from different angles. This also applies to the clinicians taking the photographs.[24]

Predictive studies included in this review suggested that artificial intelligence can determine risk stratification and the development of chronic venous insufficiency (CVI), as well as provide personalized information based on patient conditions. ML quickly generated prediction models for the prognostic questions, helping clinicians to predict the presence of vascular disease using patients' demographics and comorbidities, while significantly reducing the required time.[26,27] However, current machine learning studies in CVI still require improvements in dataset type and size to enhance data training process for critical applications, as AI algorithms cannot generate accurate predictions without comprehensive data input.[14,26]

Another AI algorithm used is natural language processing (NLP), such as chatbots like "ChatGPT", a pinnacle language model that produces human-like responses to natural language inputs. NLP has demonstrated significant benefits in healthcare, particularly in managing information overload within the medical domain—such as aggregating patient notes, analyzing treatments, and processing health records—and in supporting clinical decision-making. Although our result suggests good performance of ChatGPT in CVI management, the number of published evidence is still limited and external validation was also not performed in that study.[9] Other review article also demonstrated potential capabilities of ChatGPT in diagnosis and treatment in cardiovascular disease.[26] However, since such chatbots utilize large language model (LLM), the risk of incorporating it in clinical practice is still unclear. Known drawbacks include the potential for inaccurate and biased results, as well as the inability to distinguish between reliable and unreliable sources. Additionally, ethical considerations must be critically evaluated to ensure user safety, accuracy, and privacy.[27]

This is the first systematic review on AI applications in CVI management. However, the study is limited by the lack of homogeneous quantitative outcomes, precluding effectiveness evaluation and meta-analysis, as well as by the scarcity of relevant publications, which hinders comparisons with other reviews. Additionally, risk of bias in the included studies was assessed as high or unclear, and the number of studies for each AI technique remains limited, highlighting the need for further high-quality research.

## CONCLUSION

AI has shown significant potential in enhancing the management of CVI patients, particularly in diagnosis, prognosis, and decision-making support. The most frequently used AI type in CVI management is deep convolutional neural network (DCNN). However, further high-quality quantitative studies are needed to confirm its effectiveness.

## DISCLOSURES

### Ethical Considerations

None.


### Funding

This research did not accept any external funding sources or third-party support.


### Conflict of Interest

No conflict of interest to declare.

### Author Contribution

AR, YBSS, and KWAP contributed to building the concept, designs, analyses, and results of the manuscript. All authors prepared the manuscript and agreed for this final version of manuscript to be submitted to this journal.


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None to declare.


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