Machine Learning as a Diagnostic and Prognostic Tool for Predicting Thrombosis in Cancer Patients: A Systematic Review

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Abstract

Khorana score (KS) is an established risk assessment model for predicting cancer-associated thrombosis. However, it ignores several risk factors and has poor predictability in some cancer types. Machine learning (ML) is a novel technique used for the diagnosis and prognosis of several diseases, including cancer-associated thrombosis, when trained on specific diagnostic modalities. Consolidating the literature on the use of ML for the prediction of cancer-associated thrombosis is necessary to understand its diagnostic and prognostic abilities relative to KS. This systematic review aims to evaluate the current use and performance of ML algorithms to predict thrombosis in cancer patients. This study was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Databases Medline, EMBASE, Cochrane, and ClinicalTrials.gov, were searched from inception to September 15, 2023, for studies evaluating the use of ML models for the prediction of thrombosis in cancer patients. Search terms "machine learning," "artificial intelligence," "thrombosis," and "cancer" were used. Studies that examined adult cancer patients using any ML model were included. Two independent reviewers conducted study selection and data extraction. Three hundred citations were screened, of which 29 studies underwent a full-text review, and ultimately, 8 studies with 22,893 patients were included. Sample sizes ranged from 348 to 16,407 patients. Thrombosis was characterized as venous thromboembolism ($n = 6$) or peripherally inserted central catheter thrombosis ($n = 2$). The types of cancer included breast, gastric, colorectal, bladder, lung, esophageal, pancreatic, biliary, prostate, ovarian, genitourinary, head–neck, and sarcoma. All studies reported outcomes on the ML's predictive capacity. The extreme gradient boosting appears to be the best-performing model, and several models outperform KS in their respective datasets.

Keywords
- thrombosis
- cancer
- machine learning
- artificial intelligence
- risk assessment

Cancer-associated thrombosis is a common occurrence, and cancer treatments, including chemotherapy, surgery, and hormonal therapies, can increase the risk of thrombosis further.[1] Thrombosis, typically venous thromboembolism (VTE)[2] is primarily characterized as deep vein thrombosis (DVT) or pulmonary embolism (PE). As of 2019, the annual incidence of VTE in cancer patients is estimated at 0.5%, compared with 0.1% in the general population.[3] Other

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analyses conclude that cancer patients have a five-to-seven-fold increased risk of developing VTE.[4] Importantly, active cancer accounts for approximately 20% of the overall incidence of VTE, which is the second most prevalent cause of death in cancer patients after the progression of the disease itself.[3] This is further underscored as fatal PE is three times more common in cancer patients in comparison to noncancer patients.[5] Intervention-wise, cancer surgery increases the risk of postoperative DVT two-fold and that of fatal PE by three-fold relative to similar procedures in noncancer patients.[6] For arterial thrombosis, Navi et al found in a retrospective analysis that the incidence rate was 4.7% in cancer patients compared with 2.2% in matched controls after 6 months.[7]

Given the elevated venous and arterial thrombosis risk in cancer patients, early detection is foundational for mitigating morbidity and mortality. Thrombosis risk stratification is key and determines the effective use of anticoagulation while balancing the risk of bleeding in each patient.[8] This can also help prevent late-term thrombosis complications such as postthrombotic syndrome, chronic thromboembolic pulmonary hypertension, venous insufficiency, and limb ischemia.[9,10] Consequently, efficient diagnostic and risk stratification techniques for thrombosis should be used to supplement current diagnostic and prognostic clinical practices in cancer patients. The current widely accepted tool for assessing the risk of VTE in cancer patients is the Khorana score (KS).[11] This metric assigns points based on cancer type, body mass index, blood counts, and treatment factors. Patients are categorized into low, intermediate, or high VTE risk, aiding the clinical discernment of this condition.[11] While KS remains the most established risk assessment model in cancer patients, it has its limitations and poor predictability in some cancer types.[11]

Machine learning (ML) learns from datasets to understand and predict disease progression, predict risk factors, examine medical images and diagnostic modalities, and suggest a disease or ailment.[12] ML has been used in assessing cancer-associated thrombosis based on its rapid and potentially accurate capabilities. Previously reported ML models included artificial neural network (ANN), linear discriminant analysis (LDA), logistic regression (LR), random forest (RF), support vector machine (SVM), and classification tree (CT), to name a few. By analyzing large pools of historical data, including patient demographics, cancer types, and treatment histories, ML models can predict which cancer patients are at higher risk of developing thrombosis, facilitating early intervention and support in clinical decision-making about thromboprophylaxis and anticoagulation.[13,14] Via ML's continuous learning and improvement as more data become available, ML's accuracy and reliability in predicting thrombosis in cancer patients can be enhanced. Consequently, the objective of this systematic review is to identify the most accurate ML model currently available in diagnosing and predicting cancer-associated thrombosis.

Methodology

Search Strategy and Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed when conducting this scoping review. Requests for access to the extracted data or the data extraction template may be provided upon contact with the corresponding author. The following databases were electronically searched for primary studies evaluating the use of ML in predicting thrombosis in cancer patients: Medline, EMBASE, Cochrane, ClinicalTrials.gov, and Google Scholar (up to September 15, 2023). A combination of search terms, "machine learning," "artificial intelligence," "thrombosis," and "cancer," were used in the literature search. For consideration, papers had to be written in English, should be primary studies including adults at least 18 years old, and with results for an ML model used to predict thrombosis following cancer.

Study Outcomes

Outcomes of interest included specificity, sensitivity, area under the receiver operating curve (AUC; an aggregate metric of performance including all classification metrics), and accuracy.

Screening

Literature search results were uploaded to Covidence review software (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia[7]).

Data Extraction

The author(s), publication date, study design, prevalence of thrombosis in cancer patients, initial study population demographics, and pertinent results were among the data that were extracted. A table of study characteristics was created to extract and all the papers were compiled. Two independent reviewers assessed all of the studies' quality using the Newcastle–Ottawa Quality Assessment.

Results

A total of 300 total citations were screened primarily through a title and abstract stage by two independent, blinded reviewers ("A.H.E-S." and "S.C."; ►**Fig. 1**). A third independent reviewer ("M.O.") resolved conflicts. In total, 271 studies were excluded, with 29 studies undergoing a full-text screening stage by A.H.E-S. and M.O. Reviewers excluded studies that did not provide data or failed to meet the inclusion criteria. Overall, eight studies that discussed the use of ML for the diagnosis and prognosis of thrombosis in cancer patients[15–22] were included. These studies examined a total of 22,893 patients. The types of cancer investigated included breast, gastric, colorectal, bladder, lung, esophageal, pancreatic, biliary, prostate, ovarian, genitourinary, head–neck, and sarcoma.[15–22] Thrombosis was characterized as VTE ($n = 6$), or peripherally inserted central catheter (PICC) thrombosis ($n = 2$). All studies reported outcomes on the

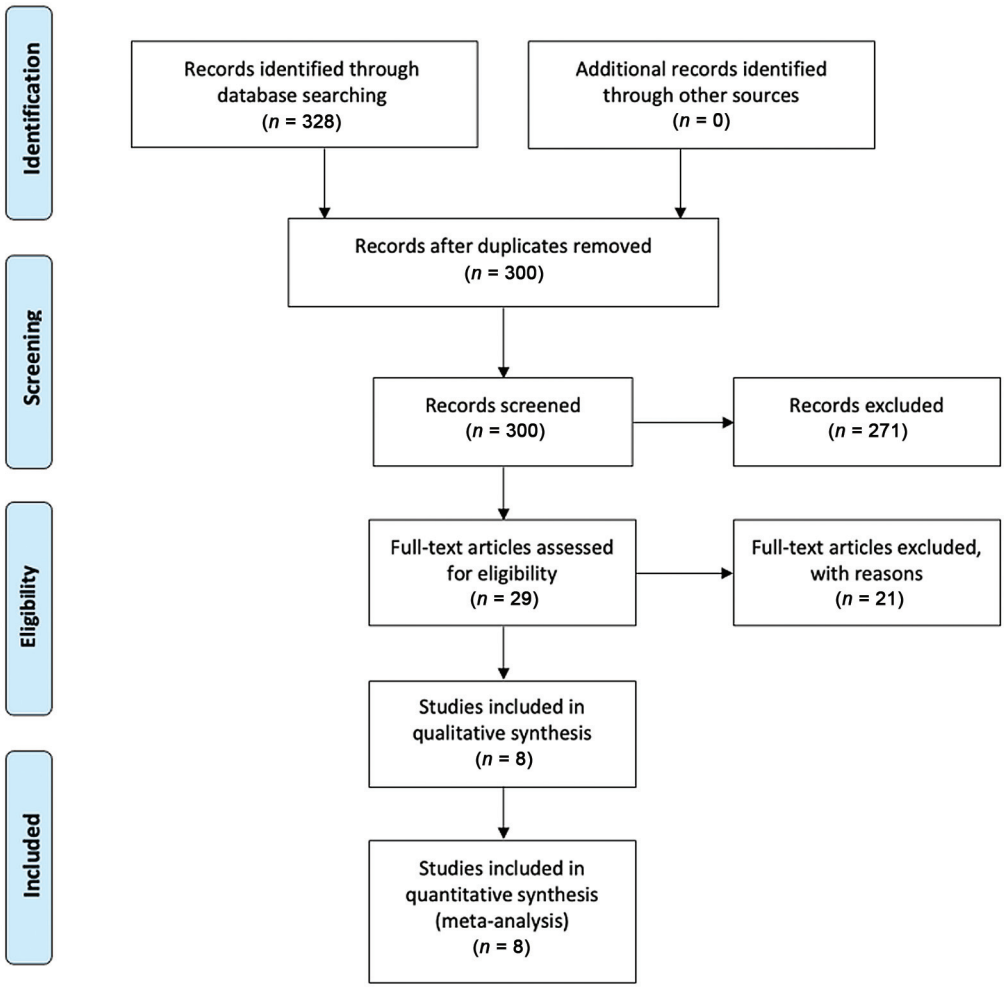

Fig. 1 PRISMA diagram. All citations from Medline, Embase, Cochrane, and ClinicalTrials.gov were uploaded and screened on Covidence in accordance with PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

ML's predictive capacity. Study characteristics and study findings are summarized in ►**Tables 1** and **2**, respectively.

Venous Thromboembolism

Ferroni et al implemented an ML model integrating kernel ML and random optimization techniques for the prognosis of VTE risk in cancer patients receiving chemotherapy.[16] This model was developed using a dataset of 1,433 cancer patients (825 patients for training, 608 patients for testing) and its efficacy was compared against the conventional KS. Results revealed that the ML model demonstrated superior performance in VTE risk prediction compared with the KS.[16] Specifically, the ML model achieved a positive likelihood ratio (+LR) of 2.30, indicating a moderate detection of patients at high risk for VTE. The negative likelihood ratio (−LR) was 0.46, suggesting improved identification of low-risk patients.[16] Additionally, the hazard ratio for VTE was found to be 4.88 (95% confidence interval [CI]: 2.54–9.37), significantly higher than that predicted by the KS (+LR: 1.58; −LR: 0.96).[16] The study reported that 7.1% of the patients (43 out of 608) were diagnosed with VTE, including 11 cases of PE and 32 of DVT. The median time from the start of chemotherapy to the development of VTE was 2.5 months.[16] The improved predictability of the ML approach over the traditional KS indicates its potential utility in clinical practice for better risk stratification and management of VTE in cancer patients. Another study by Ferroni et al explored the use of artificial intelligence (AI) in assessing the risk of cancer-associated thrombosis.[15] This study compared a novel ML predictor with the traditional KS. The study involved developing and validating this AI model using data from the same 608 oncology patients.[15] The ML predictor was evaluated based on its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The results showed that the ML predictor achieved a significantly higher AUC of 0.72 (95% CI: 0.68–0.75) compared with the KS's AUC of 0.55 (95% CI: 0.51–0.59).[15] In terms of sensitivity, the AI model demonstrated a rate of 67% (52–80), while its specificity was recorded at 71% (69–72). The PPV was found to be 15% (12–18), and the NPV was notably high at 97% (95–98).[15] These results indicate a substantial improvement in the accuracy of VTE risk prediction among cancer patients at low risk when using the ML approach compared with the traditional KS.[15] Overall, the study shows the potential of integrating advanced AI and ML techniques in medical risk

Table 1 Study characteristics including the machine learning used, training and validation data and the type and rate of thrombosis seen in each study

Author	Country	Study design	ML model(s)	Sample size (male:female)	Type of cancer (site and stage)	Type of thrombosis evaluated	Incidence of thrombosis	Cross-validation	Training sample size	Validation/ Test sample size	Significant risk factors
Ferroni et al[15]	Italy	Prospective	ML predictor	not available	Various solid cancers	VTE	5.70%	not available	not available	not available	not available
Ferroni et al[16]	Italy	Retrospective	ML predictor (a model incorporating the two best predictors)	1,433 to train the model (this time it is only 608). Of the 608—293 M, 315 F	Colorectal, gastric, esophageal, pancreatic, biliary, lung, breast, prostate, ovarian, genitourinary, head–neck, sarcoma, unknown, other	VTE	PE (1.8%), DVT (5.3%)	3-fold cross-validation	Of the 1,433 (825 were training)	Of the 608 (354 were testing)	Blood lipids, BMI, ECOG performance status, age
Fu et al[17]	China	Prospective	ANN	1,844	Breast cancer	Peripherally inserted central catheter-related thrombosis	PICC: $n = 256$ (13.9%)	not available	1,497	347	not available
Jin et al[18]	China	Retrospective	LDA, LR, CT, RF, SVM	1,035 (502 M, 48.5%)	Includes tumor stage I, II, III, IV, X	DVT	231/1,035 (22.3%)	10-fold cross-validation	90%	10%	Age, previous VTE history, Charlson Comorbidity Index, length of stay, D-dimer levels
Liu et al[19]	China	Prospective	LASSO and RF (LASSO-RF)	348	–	PICC-related thrombosis	16.38%	–	50%	50%	not available
Meng et al[20]	China	Retrospective	LR, SVM, RF, XGBoost	1,100 (485 M, 44.09%)	–	VTE	30.90%	10-fold cross-validation	80%	20%	D-dimer level, diabetes, hypertension, pleural metastasis, and hematological malignancies
Muñoz et al[21]	Spain	Retrospective	LR, DT, RF	16,407 (54.4% male, 45.6% female)	Colorectal, lung, bladder, breast cancer	DVT, PE, visceral vein thrombosis, synchronic PE/DVT	11.40%	Internal validation	1,668 (75%)	556 (25%)	Metastasis, adenocarcinoma, patient age, family history of VTE, and the characteristics of the thrombotic event (DVT and PE).
Xu et al[22]	China	Retrospective	RF, SVM, BPNN, NB, XGBoost, LR	3,092 (2,224 male, 868 female)	Gastric cancer	VTE including DVT and PE	VTE occurred in 105/3,092 (3.4%)	10-fold cross-validation	70%	30%	Clinical stage, blood transfusion history, D-dimer, age, and fibrinogen degradation products were identified as the top five predictors

Abbreviations: ANN, artificial neural network; BMI, body mass index; CT, classification tree; BPNN, decision tree, BP-network; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; LDA, linear discriminant analysis; LR, logistic regression; ML, machine learning; NB, Naïve Bayes; PICC, peripherally inserted central catheter; PE, pulmonary embolism; RT, random forest; SVM, support vector machine; VTE, venous thromboembolism; XGBoost, extreme gradient boosting.

Table 2 Study findings

Author	ML model(s)	AUC	Accuracy	Specificity	Sensitivity	AUC for KS
Ferroni et al[15]	ML predictor	0.72	not available	0.71	0.67	0.55
Ferroni et al[16]	ML predictor	0.72	not available	not available	not available	0.56
Fu et al[17]	ANN	0.67–0.74	0.62–0.72	0.59–0.71	0.73–0.80	not available
Jin et al[18]	LDA	0.681	0.773	0.660	0.754	0.60–0.64
	LR	0.684	0.772	0.660	0.768	
	CT	0.768	0.639	0.871	0.406	
	RF	0.806	0.660	0.929	0.377	
	SVM	0.810	0.665	0.921	0.420	
Liu et al[19]	LASSO-RF	0.809	not available	0.903	0.714	not available
	RF	0.775	not available	0.883	0.500	
Meng et al[20]	LR	0.757	0.759	0.763	not available	not available
	SVM	0.759	0.768	0.783	not available	
	RF	0.743	0.800	0.895	not available	
	XGBoost	0.818	0.845	0.888	not available	
Muñoz et al[21]	LR	0.66	0.603	not available	0.593	not available
	DT	0.69	0.673	not available	0.61	
	RF	0.68	0.628	not available	0.64	
Xu et al[22]	RF	0.784	0.827	0.840	0.451	not available
	SVM	0.825	0.799	0.802	0.710	
	BPNN	0.779	0.666	0.662	0.774	
	NB	0.803	0.729	0.730	0.71	
	XGBoost	0.756	0.750	0.756	0.581	
	LR	0.816	0.736	0.735	0.742	

Abbreviations: ANN, artificial neural network; AUC, area under the receiver operating curve; CT, classification tree; BPNN, decision tree, BP-network; KS, Khorana score; LDA, linear discriminant analysis; LR, logistic regression; ML, machine learning; NB, Naïve Bayes; RF, random forest; SVM, support vector machine; XGBoost, extreme gradient boosting.
The various ML models used in all eight studies with reported outcomes including accuracy, sensitivity, specificity, area under receiver operating curve.

assessment, particularly for predicting VTE in cancer patients.

Similarly, using ML models, Meng et al aimed to enhance VTE risk prediction in hospitalized cancer patients.[20] Analyzing data from 1,100 patients, the study employed LR, SVM, RF, and extreme gradient boosting (XGBoost) algorithms.[20] The XGBoost model emerged as the most effective, achieving an AUC of 0.818. It also demonstrated high accuracy (84.5%), precision (75%), recall (75%), and specificity (88.8%).[20] The other models, LR, SVM, and RF, exhibited slightly inferior performance metrics. Notably, the XGBoost model identified key predictive features such as D-dimer levels, diabetes, hypertension, pleural metastasis, and hematological malignancies.[20] The study's findings present the potential of advanced ML techniques in refining VTE prognosis risk assessment in a clinical setting, particularly for hospitalized cancer patients.

Muñoz et al aimed to develop an ML-based predictive model for VTE recurrence in cancer patients on anticoagulants. Utilizing electronic health records from nine Spanish hospitals, the model incorporated LR, decision tree, and RF algorithms.[21] A total of 16,407 anticoagulated cancer patients with a VTE diagnosis were analyzed. The model identified primary PE, DVT, metastasis, adenocarcinoma, hemoglobin, serum creatinine levels, platelet and leukocyte count, family history of VTE, and patient age as predictors of VTE recurrence.[21] The LR model exhibited an AUC of 0.66, the decision tree 0.69, and the RF 0.68.[21] The study's findings offer a new prognosis predictive tool for assessing VTE recurrence risk in cancer patients, potentially improving clinical management.[21]

Xu et al enhanced the prediction of VTE in gastric cancer patients. They employed a comprehensive analysis of 3,092 patients and compared the performance of five ML algorithms against conventional LR.[22] Among the algorithms, the SVM model demonstrated superior performance. It achieved a notable AUC of 0.825, indicating a high level of predictive accuracy. The accuracy of the SVM model was 79.9%, with a sensitivity of 71.0% and a specificity of 80.2%.[22] These metrics reflect the model's ability to correctly identify patients at

risk of VTE.[22] The study highlights the significant potential of ML models, particularly the SVM, in enhancing the prediction of VTE among gastric cancer patients, leading to improved clinical decision-making and patient care.[22]

Finally, Jin et al developed and validated ML models to predict cancer-associated DVT and compared these models with the KS.[18] Utilizing data from 2,100 cancer patients, of which 1,035 underwent Doppler ultrasonography, the study employed univariate analysis and Lasso regression to select significant predictors. Five ML algorithms were used: LDA, LR, CT, RF, and SVM.[18] The incidence of cancer-associated DVT was 22.3%. Among the ML models, LDA (AUC = 0.773) and LR (AUC = 0.772) outperformed KS (AUC = 0.642).[18] Inclusion of D-dimer as a predictor improved the performance across all models. The study also developed a nomogram and web calculator for the best-performing LR model to assist health care professionals in assessing individualized cancer-associated DVT risk.[18]

Peripherally Inserted Central Catheter Thrombosis

Fu et al aimed to develop a predictive model for catheter-related thrombosis in breast cancer patients.[17] This model employed a prospective cohort of 1,844 patients and compared an ANN model with traditional LR.[17] The ANN model, particularly when augmented with Synthetic Minority Oversampling Technique (SMOTE), showed superior performance. With SMOTE, the ANN model achieved an AUC of 0.742 and an accuracy of 71.5%.[17] Without SMOTE, the ANN's AUC was 0.725 with an accuracy of 64.6%. In comparison, the LR model achieved an AUC of 0.670 and accuracy of 61.7% with SMOTE, and an AUC of 0.675 and the same accuracy without SMOTE.[17] The study concluded that the ANN model, especially enhanced with SMOTE, is more effective in predicting catheter-related thrombosis in breast cancer patients undergoing chemotherapy, highlighting the potential of ML in improving clinical predictions in oncology.[17]

Liu et al aimed to assess the prognosis risk of PICC-related thrombosis in cancer patients using ML techniques.[19] It involved a prospective cohort of 348 cancer patients with PICCs, using four ML models for risk assessment comparison: RF, LASSO-RF, Seeley-LASSO-RF, and Seeley-RF.[19] Results showed the ML models' effectiveness in PICC-related thrombosis risk assessment, with AUC of 0.773, 0.787, 0.783, and 0.772, respectively.[19] These results outperformed the currently used criteria, which failed to identify any positive cases. The research confirmed the superiority of ML approaches in identifying high-risk cancer patients for PICC-related thrombosis and provided insights into predictors and risk factors of thrombosis.[19]

Discussion

This systematic review provides a comprehensive overview of supervised ML applications for thrombosis prediction in cancer patients, consolidating conclusions using all relevant knowledge to date. Reviewed literature from varied backgrounds offers diverse perspectives to further help elucidate the ability of ML in thrombosis risk assessment. This review concludes that ML has the potential to accurately predict thrombosis in cancer patients; however, more studies are needed to validate these findings for diagnostic and prognostic clinical capabilities. Future studies should focus on comparing ML to established risk score predictors, including but not limited to the KS, Wells Score for DVT and PE, and Caprini risk assessment model, which can aid in a more complete evaluation of predictive performance.

ML algorithms recognize relationships within datasets and have the ability to use past inputs to analyze future inputs more accurately.[23,24] Thrombosis risk in cancer patients can be predicted by ML algorithms through analyzing clinical and genetic data, thus predicting the likelihood of thrombotic events.[25] Notably, this dynamic approach allows for greater personalization among cases, capturing subtleties that traditional risk scores may miss.

The distinction between ML and conventional risk score predictors lies in adaptability. Traditional risk score predictors utilize common clinically assessed variables, whereas the integration of supervised learning algorithms generates greater opportunity for the derivation of unique and more accurate predictions.[26] With this, ML applications are becoming increasingly diverse. While promising, there remains the requirement to evaluate interpretability and clarity of output, encouraging continued refinement.[27] Additionally, generalizability of findings must be tested against evolving cancer types, treatment histories, and patient profiles, to ensure externally valid outcomes and maintain clinical relevance.[28]

With the consensus on the clinical utility of established risk scores compared with ML remaining varied, this review highlights studies that advocate for the superiority of ML models in terms of predictive accuracy, while acknowledging the challenges of clinical implementation and the need for further research. ML has become a realistic next step for risk prediction; however, the heterogeneity in the ML algorithm array underscores the complexities of evaluating each model in comparison with one another in the near future.

Limitations of this review are primarily associated with the nature of the included studies. The inclusion of all studies examining adults with any cancer type opens the opportunity for variability in the evaluation within each study. This presents a multitude of variables that are unable to be controlled to the same degree, thus discretion is needed when filtering through any conclusions made. Factors such as an insufficient sample size and variabilities in methodologies, introduce biases when drawing definitive conclusions. These limitations emphasize the importance of exercising caution when interpreting these results, further highlighting areas for improvement in future research studies.

Future research endeavors may benefit by employing a greater focus on comparisons between ML algorithm types, highlighting the advantages and disadvantages of each in the context of clinical applications. Advancing current literature in thrombosis prediction requires the exploration of novel methods, allowing this avenue to be deemed appropriate. The inclusion of studies with larger and more diversely stratified cohorts would enhance the quality of findings

while improving generalizability of ML models across populations; given the relevant studies were conducted in China, Spain, and Italy, limiting geographical generalizability. Once the best-performing ML model is determined and the application of ML is ascertained as favorable, analyzing feasibility of implementation in clinical settings is critical. Establishing practical utility in addition to obtaining professional opinions on ML implementation will provide a valuable angle to this research. The perspectives of clinicians and industry professionals can impart a unique outlook; translating these findings into a patient-centric adaptive framework.

The deployment of ML for the clinical diagnosis and prognosis of thrombosis in patients with cancer is impeded by several additional challenges.[29] A primary obstacle is the scarcity of large and diverse datasets that accurately capture the complex characteristics of cancer and patient profiles, which is essential for training accurate ML models.[29] The heterogeneity in cancer types, treatment regimens, and thrombosis incidence complicates the development of universal predictive models. Moreover, the variety of available ML tools and methodologies, although advantageous for innovation, hinders the uniform application and integration of these technologies into existing clinical processes.[29] Additionally, the incorporation of ML into health care is further limited by the lack of sufficient training for physicians and health care providers on effectively using these advanced tools, undermining their confidence in ML-driven insights.[29] Addressing these challenges requires a focused effort on enhancing data collection and promoting educational initiatives to fully realize the potential of ML in predicting cancer-associated thrombosis.

Conclusion

This review has highlighted the promising role of ML in predicting thrombosis in cancer patients, presenting its potential to outperform traditional risk assessment models. This adaptability and precision in risk assessment could lead to more effective early interventions, ultimately enhancing patient outcomes. However, the variability in methodologies, sample sizes, and types of ML algorithms used across studies necessitates a cautious interpretation of these findings. This review reveals a need for more extensive research to validate ML models' effectiveness and compare them against current established risk score models.

Data Availability

All data are available upon request to the corresponding author.

Conflict of Interest

None declared.

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