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Machine learning in cancer-associated thrombosis: hype or hope in untangling the clot

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Abstract

The goal of machine learning (ML) is to create informative signals and useful tasks by leveraging large datasets to derive computational algorithms. ML has the potential to revolutionize the healthcare industry by boosting productivity, enhancing safe and effective patient care, and lightening the load on clinicians. In addition to gaining mechanistic insights into cancer-associated thrombosis (CAT), ML can be used to improve patient outcomes, streamline healthcare delivery, and spur innovation. Our review paper delves into the present and potential applications of this cutting-edge technology, encompassing three areas: i) computer vision-assisted diagnosis of thromboembolism from radiology data; ii) case detection from electronic health records using natural language processing; iii) algorithms for CAT prediction and risk stratification. The availability of large, well-annotated, high-quality datasets, overfitting, limited generalizability, the risk of propagating inherent bias, and a lack of transparency among patients and clinicians are among the challenges that must be overcome in order to effectively develop ML in the health sector. To guarantee that this powerful instrument can be utilized to maximize innovation in CAT, clinicians can collaborate with stakeholders such as computer scientists, regulatory bodies, and patient groups.

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Keywords

cancer-associated thrombosis; venous thromboembolism; machine learning; natural language processing

Introduction

Cancer-associated thrombosis (CAT) is now a well-established disease entity and is recognized to substantially impact the overall survival, morbidity, quality of life and healthcare costs of the cancer subpopulation.[1–3] Management of cancer itself has evolved rapidly since CAT was first described in the 1800s, with major breakthroughs in surgical, radiation and medical interventions. However, data suggest that the rates of CAT continue to rise perhaps reflecting improving diagnostics and/or increased survival in patients with cancer, including patients treated with novel therapeutic agents such as targeted agents and immunotherapies.[4,5] Moreover, despite the advances in cancer treatment, venous thromboembolism in patients with cancer continues to be associated with increased mortality in contemporary cohorts.[6,7]

Machine learning (ML) refers to a specialized field of computer science that leverages algorithms to automatically identify patterns in data and ultimately perform a task. This approach has led to numerous transformative applications in diverse fields from voice recognition to virtual assistants, traffic prediction, financial market analysis and forecasting, fraud/criminal recognition and even self-driving vehicles.[8] Considerable interest exists in developing applications of ML in healthcare to enhance diagnostic accuracy, improve efficiency, safety and quality, and substantially offload physicians. However, the high stakes inherent to healthcare as well as limitations intrinsic to ML science bring about somewhat unique challenges to its implementation in medicine, tempering enthusiasm and progress.[9,10] It is essential that clinicians work in close partnership with computer scientists to ensure that ML models developed are practical, unbiased and meet standards required to be integrated into patient care.

Applications for ML in the arena of hemostasis and thrombosis are growing. In this review, we catalog the potential areas where ML can enhance clinical care for patients with thrombotic disorders, with a focus on CAT. We also briefly review future directions and pitfalls that researchers and clinicians will need to be cognizant of as these technologies grow from research projects to more practical applications in the clinic.

Opportunities for application of machine learning to prevention and treatment of cancer-associated thrombosis

Certain features of thrombotic disorders may make these diseases particularly suitable to apply ML.[11] A training dataset is a large pool of data used to adjust a ML model's parameters and learn the underlying patterns in data; subsequently, the model is tested on an independent dataset to test its performance, known as validation dataset. Thrombotic conditions are relatively common and thus curating real-world datasets for training and validation of ML models is potentially feasible. Moreover, thrombosis is a frequent complication in cancer patients and feature-rich datasets already exist that could be targeted to develop and use ML models.[12,13]

Secondly, although the precise etiology of thrombosis in individual patients can be hard to pinpoint, there are several potential factors that are often available in electronic health records contributing to the risk of thrombosis and thus can be used as 'features' in ML models. Risk factors for CAT are extremely diverse and range from patient factors, (such as age and habitus), tumor features (such as site and stage), laboratory values, interventions (including surgery and procedures) as well as systemic medications (including cytotoxic chemotherapy, hormonal therapy and targeted agents).[14]

The interventions used to prevent and treat thrombotic disorders usually involve anticoagulants, and thus bleeding risk needs to be balanced in patients with or at risk for thrombosis. Models based on ML can be envisioned to be developed not only to calculate risks associated with thrombosis but also bleeding and thus facilitate informed and tailored decisions for clinicians and patients. Patients with cancer are not only at increased risk of thrombosis but also have high rates of major and fatal bleeding, which makes anticoagulation a challenge for clinicians.[15,16] Finally, patients with malignancy are relatively complex and can have significant temporal changes in thrombotic and hemorrhagic risk factors due to changes in cancer status (disease progression/recurrent or metastatic disease in critical sites), alterations in therapeutic interventions and general health status leading to institutionalization or immobilization. Thus, CAT risk is dynamic and continuous risk assessment would be beneficial to account for variations in risk with time.[17]

We identified three specific applications of ML to the research and clinical management of thromboembolism: i) natural language processing to optimize automated identification of thrombotic complications in patients; ii) computer vision to classify radiology images; iii) predictive ML modeling for thrombosis (Figure 1, Table 1).

Natural language processing and venous thromboembolism

Natural Language Processing (NLP) refers to the application of ML technology and linguistics to enable computers to automatically interpret, manipulate, and comprehend human language.[18] Within healthcare, this allows automated interpretation of textual data within the electronic health record such as those in medical notes or laboratory and radiological reports for accurate case detection that can, in turn, aid surveillance efforts, augment hospital triage systems, and allow for automated measurement of quality metrics.[19] For computers to analyze human language, one can rely on keyword extraction, predetermined rule-based technology or more advanced techniques that apply ML algorithms to make inferences, all approaches which have been studied in text into case-detection algorithms in the electronic health records.[20] Furthermore, with the advent of generative artificial intelligence technology, such as generative pre-trained transformer (also known as GPT) models, there is interest in developing NLP applications to reduce burdens and time for providers by assisting in tasks such as automation of documentation with human review, prepare orders or compute and synthesize information from electronic health records and medical literature.[21,22]

The application of NLP for the detection of thrombotic disorders including deep vein thrombosis (DVT) and pulmonary embolism has been developed for over a decade.[23–26] Although manual extraction is considered the gold standard, this labor-intensive process is not feasible for long-term and continuous case extraction. The use of billing or administrative diagnostic codes lacks accuracy for VTE detection and compares unfavorably to NLP algorithms.[27] In a multicenter study that compared NLP to manual chart extraction in two orthogonal datasets, the NLP-based VTE identification system was found to score >90% on all performance measures calculated including accuracy, sensitivity, specificity, and positive and negative predictive in both datasets.[28] This supports that NLP could be a promising tool for automated surveillance systems. This technology has also been studied for VTE surveillance in specific settings such as post-surgery, pediatric populations and patients hospitalized with COVID-19.[29–31]

Various researchers have worked on developing NLP models that can aid acute CAT case detection within cohorts of patients with malignancy. Ostensibly CAT may differ from thrombosis in the general population given higher patient complexity, cancer-directed medications, more frequent interventions such as central access catheters as well as the high prevalence of preexisting thrombosis which could make detection of recurrent acute events challenging. A transformer NLP model utilizing a combination of clinical notes and radiology reports to detect CAT longitudinally was developed that achieved a precision (positive predictive value, PPV) and recall (sensitivity) of about 93%.[32] A separate group demonstrated the successful use of a customized NLP pipeline for clinical notes, used in combination with a keyword search of radiology reports and extraction of anticoagulation data from pharmacy records to detect VTE events in 14,223 adult patients with solid tumor malignancy.[33] Li *et al.* used a longitudinal single-center retrospective dataset of patients with cancer to demonstrate that a combined algorithm based on billing codes and anticoagulation with a ruled-based NLP classifier had a weighted PPV of 98% and a weighted sensitivity of 96%, with a C statistic of 0.98 (95% CI, 0.97–0.98) that out-performed either approaches individually.[34] This suggests that combining information related to VTE from both structured data (billing and procedural codes and laboratory results) and unstructured data (such as radiology reports, clinical notes) could lead to optimal event detection. The use of NLP to detect thrombotic events in more specific oncologic populations such as patients undergoing allogenic stem cell transplants has also been described.[35]

Machine learning applications for image recognition in venous thromboembolism

Diagnosis of VTE is routinely established by radiological investigations including computed tomography angiograms, pulmonary ventilation perfusion scans and duplex ultrasound for extremity DVT.[36] This is performed historically with trained physicians reviewing imaging visually to identify pathologies and make diagnoses. The field of computer vision leverages ML algorithms to recognize patterns in imaging data fields that exceed the limits of the human eye. Those models can be integrated into workflow to improve efficiency.[37] Moreover, within oncology, ML offers the ability to optimize image acquisition sequences to maximize efficiency and reduce radiation exposure and costs, develop personalized screening programs for patients, create precise and reliable volumetric-based tumor responses to guide cancer-directed therapies and potentially elucidate otherwise imperceptible radiographic patterns to investigate cancer biology, as well as predict treatment response (also known as 'radiomics').[38]

Given that pulmonary embolism can be clinically misdiagnosed or missed in up to one-fourth of patients,[39] several groups have worked on ML-based automatic detection models for this clinical event.[38,40,41] A deep learning model (PENet) for automatic detection of pulmonary embolism from volumetric computed tomography (CT) pulmonary angiograms was developed that achieved an AUROC of 0.85 [95% CI 0.81–0.87] on an external dataset.[42] Such tools can be envisioned to serve as secondary reading tools and also prioritize scans in radiologist review queues to prevent delays in diagnosis. Beyond the detection of PE, deep learning-based models to quantify clot burden are also being developed that have been shown to correlate with risk stratification markers in acute pulmonary embolism, including right ventricular metrics.[43,44] Similarly, ML-based tools have been developed for computer-aided diagnosis of DVT, although the majority utilize MR/CE-MRI or CT-venography, while the most widely employed diagnostic technique is compression ultrasound.[45–48] Aiming to equip non-specialists to detect DVT, a deep learning approach to compression ultrasound images was developed and externally validated with a negative predictive value of 98–99%. The authors also performed a cost analysis of integrating this ML tool into their current diagnostic pathway and estimated the net monetary benefits.[49]

Studies exploring the role of ML-assisted radiologic diagnosis of pulmonary embolism, extremity-associated vein thrombosis and thrombosis in unusual sites such as splanchnic and cerebral vasculature specifically in patients with underlying cancer are pending. However, several potential uses of ML-assisted radiological imaging at several stages in the cancer journey including screening, disease detection, treatment assessment and surveillance have already been identified.[50] Surveillance imaging is frequent among patients with malignancy, and ML could assist in automated detection of thrombosis in patients where a diagnosis is not otherwise suspected. Estimating the composition of thrombus using artificial intelligence is also an emerging method that has shown to be potentially impactful for prognostic and therapeutic decision-making in ischemic stroke.[51] Such an approach can be envisioned in CAT for determinations that have therapeutic significance such as to differentiate chronicity of a thrombus as well as distinguish between bland thrombus and intravascular involvement by tumor.[52,53]

Machine learning for prediction of cancer-associated thrombosis

Modeling the risk of CAT is a potentially impactful application of ML given the importance of risk stratification for prophylaxis. The yearly risk of CAT is relatively low overall, with a cumulative incidence of less than 10% in most reports.[54] Anticoagulant prophylaxis in this patient population has not been shown to be associated with a significant increase in the risk of major bleeding overall, however specific subgroups might have a higher risk.[55] Monetary costs and inconvenience for patients constitute additional downsides of pharmacological prophylaxis. In order to maximize net benefit, it is desirable to carefully select candidates for thromboprophylaxis, focusing on individuals with the highest risk of thrombosis and the lowest risk of bleeding. ML predictive models could conceivably be applied to both sides of this equation in order to optimize preventive efforts.

The first broadly used risk stratification algorithm for CAT is the Khorana score.[56] Still very prevalent in the clinical arena, this clinical prediction rule is derived from a simple logistic regression model. It is easy to use and has been extensively validated.[57] It has been applied in randomized studies of pharmacological prophylaxis for CAT, in which a clinical benefit was demonstrated in the intervention group.[58] However, in general, the Khorana score has exhibited disappointing performance. It does not have an appreciable capacity to discriminate thrombosis risk within cancer strata, as the most important predictor in this model is tumor type. Using a score threshold of 2, typically half of patients in a diverse solid cancer cohort will be retained for prophylaxis, however, left untreated less than 10% of those individuals would go on to develop a CAT episode by the 6-month mark.[57]

Based on those considerations it becomes evident that improved CAT prediction models are needed. Beyond additive models like logistic regression, more advanced algorithms could conceivably improve model discrimination and accuracy by leveraging complex relationships between predictors. Also, doing away with the clinical prediction rule format and switching to a model deployed directly from the electronic health record would allow the inclusion of a far greater number of predictors than otherwise possible, along with more granularity in model inputs.

In the last few years, several authors have explored varied ML algorithms to improve risk prediction for CAT. The approaches used include additive models (*e.g.*, logistic regression and Fine-Gray regression), tree-based models (*e.g.*, random forests), kernel methods (*e.g.*, support vector machines), gradient boosting, ensembles and deep learning.[59–69] The predictors featured in those models included cancer type and stage, routine laboratory test results (*e.g.*, hemoglobin, total white blood cell count, *etc.*), basic demographic characteristics, chemotherapy type, circulating procoagulant vesicles, circulating tumor DNA levels, germline molecular markers and tumor somatic genetic alterations. As a general rule, model discrimination as measured with the C-index did not surpass 0.72 in the test set. External validation is lacking for most of those studies, with few instances of a satisfactory assessment.

While the findings above are stimulating, much remains to be done to change the paradigm of CAT prediction and prevention. At this juncture, it appears unlikely that more complex modeling algorithms using the usual static risk markers will improve model metrics. Incorporating large amounts of omics data, unstructured data, novel orthogonal biomarkers or time series data of predictors commonly available in the electronic health record are all approaches with the potential to move the needle further and meaningfully increase the net benefit of pharmacological prophylaxis for CAT. Survival methods could generate CAT incidence predictions which factor in the competing risk of death, allowing the clinician to estimate risk at different arbitrary time points. Deep learning models can be customized extensively and offer the added benefit of transfer learning but are more technically difficult to implement and require larger datasets than other ML algorithms to reach their full potential. Model generalizability between locales will remain a challenge and federated learning is a promising modality to alleviate privacy concerns surrounding the sharing of multiple large patient datasets.

Future challenges for the application of machine learning to clinical management of cancer-associated thrombosis

Despite the exciting avenues for ML in clinical medicine, researchers and clinicians involved in the development of this novel technology need to be mindful of challenges and potential pitfalls (Table 2).[9,53] Although electronic health records do contain enormous amounts of data that could be relevant to CAT, these are often unstructured and siloed in medical imaging archival systems, pathology systems, documentation fields, electronic prescribing tools and insurance databases which would need to be processed and unified so they are accessible to an algorithm. Moreover, datasets for most current ML studies in VTE are retrospective and fixed; however, in reality, a ML model for thrombosis would need to handle non-stationary input data due to changes in clinical, operational practices as well as dynamic patient populations and changing individual health status. Thus, methods to address dataset shift and update models prospectively would need to be built in beforehand to ensure optimal performance.[70] Prospective testing of these computer systems and periodic or continuous performance checks are also critical to ensure the models remain accurate despite changes in the environment, to detect issues and deploy updates to address them.

Generalizability, so that tools can be utilized outside their training environments, is an important goal in developing ML applications.[71] Moreover, ML algorithms that operate without human oversight can be prone to over-fitting or utilization of unknown confounders that would not be reliable in a different setting or dataset.[72] Given that, different institutions can vary widely in clinical practices, record keeping, and technical equipment; this can be a particular challenge in building tools for widespread clinical use. Transfer learning is a ML technique that allows computer systems to apply knowledge learned from a task to be reused to improve performance on related tasks. This can save computing and time resources, and thus can be lever-aged to enhance generalizability.[73] Another attractive approach that has emerged to improve generalizability is federated learning. Federated learning can be used to derive a global model from several distinct datasets belonging to different organizations without sharing sensitive clinical data between the participants, thus preserving patient privacy.[74]

A serious concern is that ML algorithms can contain discriminatory biases, that can inadvertently affect already disadvantaged groups in healthcare and enhance health inequities.[75,76] In order to avoid unintentional bias in ML algorithms that could further worsen existing racial and ethnic disparities in CAT, developers need to be sensitive of potential issues in the databases where the models are trained.[77,78] Clinicians should also be mindful of testing and evaluating models by population subgroups (such as race, age, socioeconomic strata, or location) before they are deployed. Moreover, rigorous regulatory frameworks need to be developed and updated in pace with technological innovation to ensure guardrails are in place for the supervised and controlled development of clinical ML models.[79,80] Towards this goal, the World Health Organization recently outlined six key areas for regulation of AI in health including transparency, risk management, data validation, data quality, privacy and collaboration between various stakeholders including regulatory agencies, healthcare providers and industry partners.[81]

There is also concern about reluctance and mistrust among clinicians and patients that can be a hurdle to the uptake of ML at the bedside. The explainability of a model can be viewed as its inner mechanics and behavior being interpretable and understandable by human observers. Deep learning models in particular often feature a large number of parameters which in isolation do not have any well-defined meaning, which can lead to a perception by users that the algorithm is a “black box”, which can decrease confidence in its accuracy and reliability. A nationally representative online panel of patients was surveyed and found that over half believed that artificial intelligence would improve healthcare delivery.[82] In a study of paired surveys of clinicians and informaticians that focused specifically on diagnosis and prevention of VTE, a majority of clinicians (70%) and informaticians (58%) indicated that they believed that AI can ensure appropriate VTE in hospital prophylaxis. However, lack of transparency was the most frequently cited barrier by both clinicians and informaticians to the use of AI in clinical care of thrombosis.[83] Finally, ensuring that ML-based tools built for CAT are adequately and rigorously studied prospectively with clinically meaningful endpoints (such as recurrent thrombosis, major bleeding and mortality) prior to deployment in clinical practice will be essential to ensure that these tools are relevant and safe in healthcare and improve patient and physician trust in their use.

Conclusions

ML has the potential to create impactful changes in clinical medicine including cancer-associated thrombosis. NLP can facilitate VTE case detection from unstructured fields including clinical notes and radiological reports to enhance research and surveillance activities. Computer vision can optimize detection of thrombotic events from radiological data which can decrease missed diagnosis and assist radiologists in triaging studies to avoid treatment delays. Finally, ML algorithms are being developed to accurately predict patients’ risk of developing CAT, which could in turn be utilized to assign thromboprophylaxis to patients who would benefit from this intervention and avoid exposing individuals with a higher bleeding risk to unnecessary anticoagulant administration. Experts and clinicians need to familiarize themselves with this novel technology to ensure that tools being developed are relevant, safe and minimize the risks of inherent bias during development. ML needs to be tested for safety and clinically relevant outcomes under the emerging regulatory landscape that can ultimately promote safe and effective innovation. Lastly, the ML models need to be continuously monitored and periodically retrained.

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Conflict of interest:

RP reports consultancy with Merck. JIZ reports prior research funding from Incyte and Quercegen; consultancy for Sanofi, CSL Behring, and Calyx. SM has served as an advisor for Janssen Pharmaceuticals and is the principal owner of Daboia Consulting LLC. SM has served as an advisor for Janssen Pharmaceuticals and is the principal owner of Daboia Consulting LLC. SM and RS have a patent application pending for VTE prediction models not featured in this review. SM has a patent application pending and is developing a licensing agreement with Superbio.ai for NLP software not featured in this review.

Availability of data and material:

no new data were created or analyzed in this study. Data sharing is not applicable to this article.

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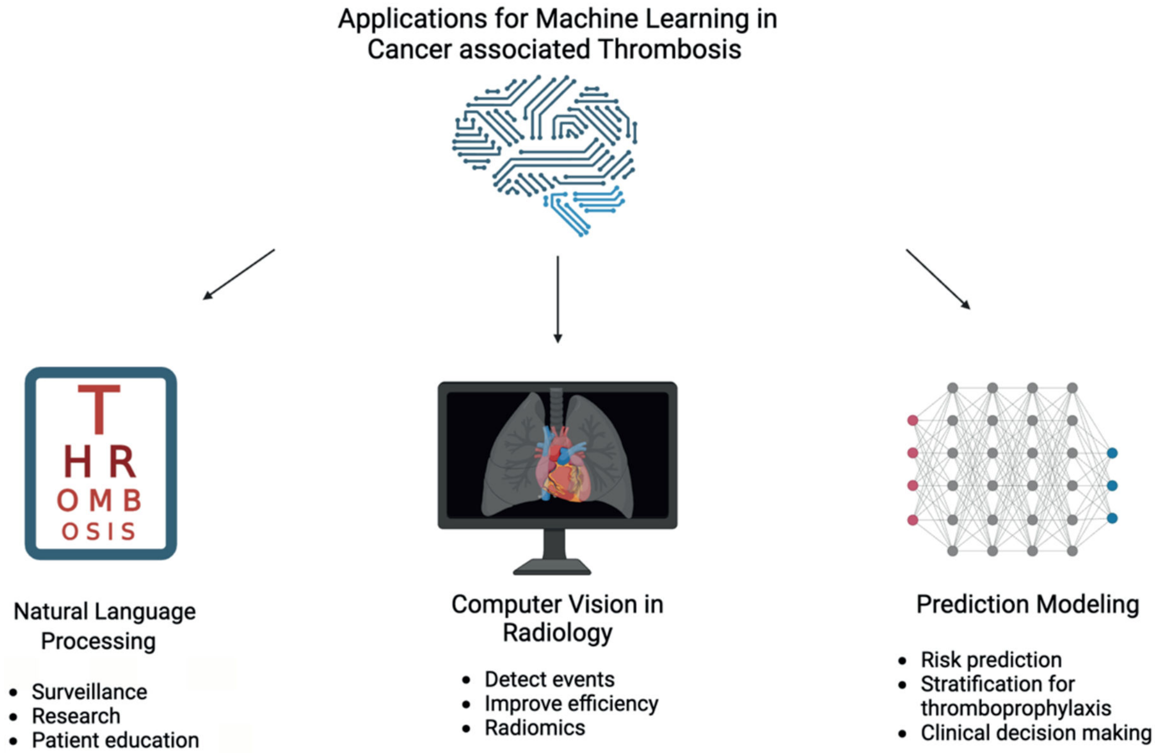

Figure 1.

Applications for machine learning in cancer-associated thrombosis.

Table 1.

Selected examples of applications of machine learning in cancer-associated thrombosis.

Study	Population/study design	Dataset size	Corpus datasets	ML model	Precision/PPV	Recall/ sensitivity	Metrics C-statistic	NPV	Specificity
Natural language processing and venous thromboembolism									
Maghsoudi *et al.*[32]	Single center; retrospective		Clinical notes; radiology notes	ClinicalBERT (Bidirectional Encoder Representations from Transformers) large language model	0.93	0.93	-	-	-
Dunbar *et al.*[33]*	Single center; retrospective		Clinical notes	Custom NLP	-	-	-	-	-
Li *et al.*34‡	Single center; retrospective		Radiology notes	Rule based NLP pipeline	0.98	0.96	0.98		-
Computer vision to identify thrombotic events from radiologic data†									
Huang *et al.*42†	Retrospective study included internal and external datasets		CT pulmonary angiography scans	3D CNN (PENet)	-	-	.84 (Internal) .85 (external)	-	-
Li *et al.*84†	Retrospective multicenter study		CT pulmonary angiography scans	CNN + U-NET	-	-	0.93	-	-
Kainz *et al.*49†	Prospective study included internal and external cohorts		Ultrasound videos	Dual-task CNN (AutoDVT)	-	0.82–0.94 (95% CI)	-	0.99–1.00 (95% CI)	0.70–0.082 (95% CI)
Machine learning based prediction modeling for venous thromboembolism									
Ferroni *et al.*59†	Retrospective	608	Tabular	Kernel method	-	-	0.72	-	-
Li *et al.*64†	Retrospective	Derivation: 9,769 validation: 79,517	Tabular	Logistic regression	-	-	0.68 (0.67–0.69)	-	-
Muñoz *et al.*[66]	Retrospective; goal was to predict recurrent VTE	16,407	Tabular	Logistic regression and decision trees (individual trees and random forests)	-	-	0.68 (0.63–0.72) for random forests	-	-
Verstovsek *et al.*68††	Retrospective	Derivation: 1,012 validation: 100	Tabular	Decision trees individual trees and random survival forests)	-	-	0.84	-	-

*Model was used to supplement an approach using pharmacological data for therapeutic anticoagulation to identify thrombotic episodes. Performance measures not reported;

‡algorithm combined billing codes and NLP on radiology reports. Combined approach was found to be better than and NLP or coding algorithm alone;

†did not describe separately patients with cancer;

††neutrophil percentage, lymphocyte percentage and red blood cell distribution width are important predictors in decision trees. ML, machine learning; PPV, positive predictive value; NPV, negative predictive value; NLP, natural language processing; CT, computed tomography; CNN, convolutional neural network; DVT, deep vein thrombosis; CI, confidence interval.

Table 2.

Key barriers to building machine learning applications in healthcare.

Barriers	Comments
Dataset quality	Feature rich, well annotated high-quality datasets need to be developed and made publicly available to train models. Testing datasets would ideally be prospective and external to establish validity.
Evolution of medical care and patient populations over time	Predictive and diagnostic models in clinical use should be audited periodically to ensure persistence of satisfactory performance metrics. Transfer learning and other model updating techniques can be used to fine tune an older model.
Changes in individual patient medical condition over time	Predictive models should be used to make clinical decisions only for the time period used in the original validation studies. Dynamic modeling should be explored to mitigate loss of predictor information over time.
Generalizability	Models need to be developed and validated on diverse datasets to ensure performance is unform across institutions and networks. Transfer learning and Federated learning can be incorporated to ensure generalizability.
Bias	Preexisting biases within datasets and clinical practice need to be identified to ensure algorithms are not flawed. Machine learning applications need to be evaluated in population subgroups to compare performance.
Regulatory framework	Regulatory agencies should work with stakeholders to establish guardrails that can keep up with technology updates t to ensure innovation is safety, efficacy and health equity
Clinicians mistrust/reluctance	Increased transparency, robust external and prospective validation to establish efficacy and safety and patient and physician education as well as effective and open regulation