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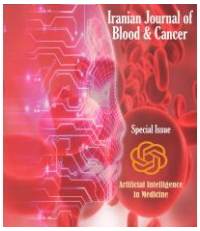

Review

The application of artificial intelligence (AI) in the diagnosis of platelet disorders

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Abstract

Artificial intelligence (AI), machine learning, and deep learning are emerging technologies with the potential to revolutionize the diagnosis and treatment of various diseases, ranging from cancer to cardiovascular disorders. These advanced algorithms have the ability to learn patterns and associations, enabling them to make predictions and enhance therapeutic approaches. Among the conditions that can benefit from AI's capabilities are platelet disorders, which at least in some cases may lead to life-threatening excessive bleeding. The conventional methods to diagnose these disorders mainly rely on manual or automated blood cell counting and morphology analysis that are prone to errors. In recent years, researchers have turned to machine learning models to predict platelet disorders, including drug-induced immune thrombocytopenia (DITP), sepsis-associated thrombocytopenia (SAT), immune thrombocytopenic purpura (ITP), disseminated intravascular coagulation (DIC), as well as thrombocytosis. These studies have yielded promising results, demonstrating satisfactory efficacy and accuracy. Our analysis revealed that key predictive parameters include the patient's medical history, platelet counts, and coagulation factors. Notably, the support vector machine (SVM) algorithm exhibited the highest performance in predicting platelet disorders, achieving the highest accuracy score while analyzing a relatively lower number of parameters.

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1. Introduction

Platelets are one of the essential cells in blood circulation able to take part in hemostasis, angiogenesis, and even immunity and inflammation (1). They originate from the differentiation of megakaryocytes in the bone marrow following the presence of transcription factors such as Runx1, c-Myb, Gata1, and Fli1 and growth factors like thrombopoietin (2). Due to the vital roles of platelets in maintaining blood vessel integrity and preventing excessive bleeding (hemostasis), any impairment in the function and or the number of platelets could lead to bleeding complications and elevated risk of thrombotic events. Therefore, platelet disorders encompass various hematological conditions characterized by defects in the function, production, and or number

of platelets (3). Accordingly, triggers causing the reduction of platelet count could lead to thrombocytopenia (4). Indeed, thrombocytopenia has been shown as one of important hallmarks of several diseases. It can also have prognostic value in pathologic conditions such as COVID-19 cases (5, 6). On the other hand, the elevation of platelet count is called thrombocythemia (if the trigger is unknown) and thrombocytosis (if the trigger is known) (7). Moreover, functional impairments of platelet often result from genetic alterations affecting specific platelet signaling pathways, receptors, or cytoskeletal components. The presence of some disorders like liver disease and uremia can lead to secondary qualitative platelet disorders which are categorized as acquired ones (8, 9). The diagnosis of platelet disorders depends on several conditions and has been performed based on several strict criteria. Although in some cases, a blood test could illustrate an overview of platelet disorders, the accurate diagnosis of platelet disorders needs a comprehensive understanding of the underlying reasons and the history of patients (10, 11). **Figure 1** was depicted to provide a general overview of the pathogenesis of platelet disorders.

Artificial intelligence (AI) is a human-made computer-based intelligence that was designed to mimic human intelligence. The AI-based systems use patterns and associations to learn how to solve problems on their own. AI could have several domains, the most important of which are machine learning and deep learning. Indeed, deep learning is the subdomain of machine learning which is based on artificial neural networks (12). Concerning medicine and medical research, the application of AI systems has been expanded to the diagnosis of several disorders and paving the way for designing therapeutic approaches (13, 14). In the current study, we illustrated how AI models can be utilized regarding platelet disorders by gathering and investigating recent articles in this context.

2. The roles of artificial intelligence (AI) in platelet disorders

AI systems have the ability to learn patterns and analyze relationships in order to make decisions. Their application in the clinical implications was initially restricted to some automatic functions in healthcare centers; however, nowadays, AI models have been utilized in order to give researchers as well as healthcare providers a way to identify diseases and detect specific biomarkers related to disorders in order to predict the early diagnosis or the prognosis of diseases (15-17). In this regard, the application of AI systems and machine learning could have roles in the diagnosis and treatment of cancers (18, 19), infections such as COVID-19 (20), metabolic disorders like diabetes (21, 22), heart failure (23-25), and blood disorders (26-29). Accordingly, researchers have utilized AI algorithms, machine learning, and deep learning systems to pave the way for the diagnosis and treatment of platelet disorders, from thrombocytopenia to thrombocythemia (11, 30).

3. The application of AI in thrombocytopenia

There are several triggers such as low potency to produce platelet, high destruction of platelets, and platelet separation able to reduce the number of platelets in the blood. Indeed, the situation in which the platelet count falls below 150,000/μL is called thrombocytopenia that could be due to liver disorders, malignancies, infections, autoimmunity, pregnancy, disseminated intravascular coagulation (DIC), coagulation diseases, and some medications (31). Lower numbers of platelet could result in impairments in bleeding control, consequently

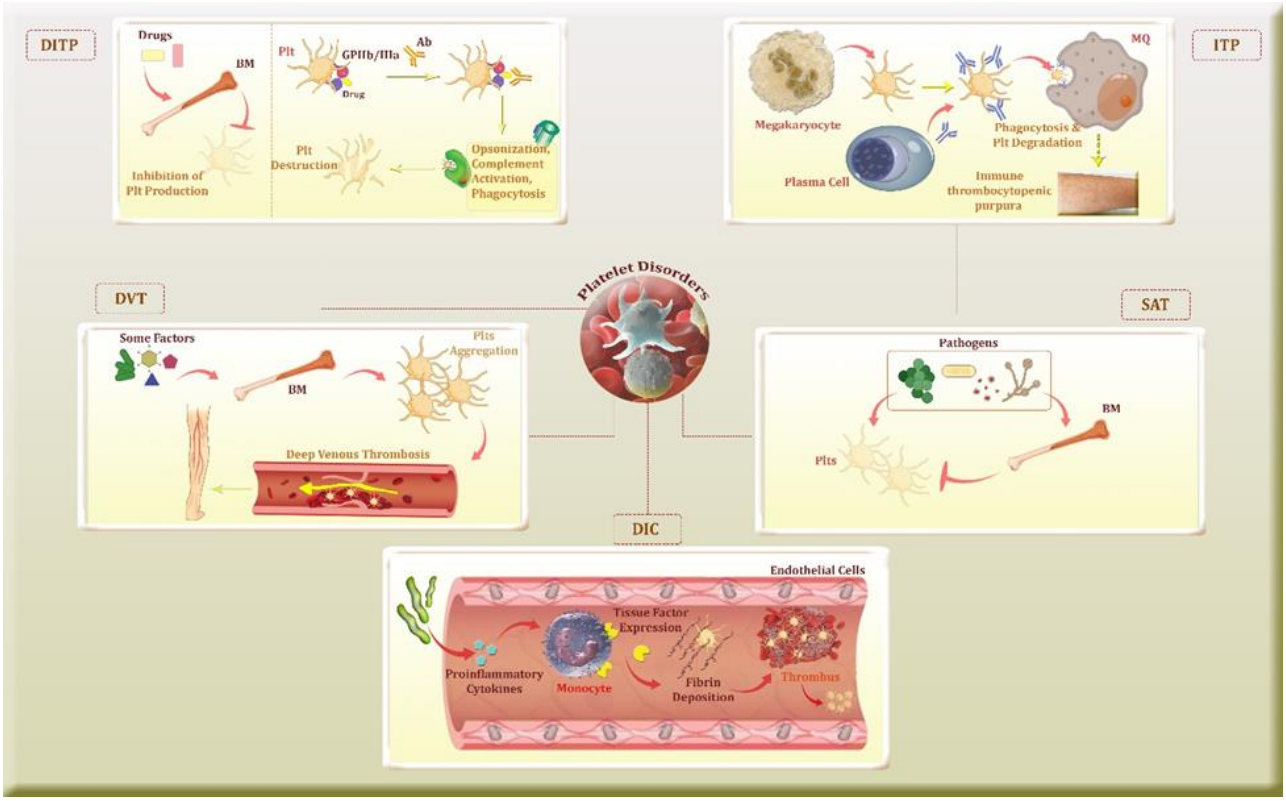

Figure 1. **The pathogenesis of platelet disorders. Platelet disorders comprise a wide range of diseases affecting either the number or the quality of platelets.** In the drug-induced immune thrombocytopenia (DITP) condition, some drugs increase the destruction or depletion of platelets. To be precise, they can influence the bone marrow and suppress the production of platelets or target the platelets directly and destroy them. In some severe conditions of infection diseases like sepsis-associated thrombocytopenia (SAT), pathogens could inhibit the production of platelets in the bone marrow. Moreover, they could lead to the over-consumption of platelets ending in platelet depletion. Regarding immune thrombocytopenic purpura (ITP), the destruction of platelets is conducted by the presence of immune reactions; particularly, anti-body-dependent platelet destruction. In the presence of some disorders including blood transfusion reactions, immune responses and inflammation, cancers, liver disorders, and sepsis, abnormal clotting could occur throughout the vessels leading to the over-consumption of platelets and clotting factors defined as disseminated intravascular coagulation (DIC). In addition to thrombocytopenic disorders, thrombocytosis could occur as a result of some agents like cancers, blood loss, and infections. In deep venous thrombosis (DVT) cases, bone marrow is affected by some factors; consequently, produces an excessive number of platelets leading to the induction of coagulation reactions and blood clots in the veins deep in the body.

causing bleeding inside the body which could be life-threatening. The early diagnosis of thrombocytopenia is crucial and is typically conducted by performing a complete blood count (CBC) test. However, other strategies such as blood smears and bone marrow tests which could be invasive should be used in order to detect the precise cause of thrombocytopenia (32). Therefore, thrombocytopenia disorders comprise a wide range of diseases; however, not all of them have been evaluated for the roles of AI.

3.1. Drug-dependent thrombocytopenia

A vast range of medications such as abciximab, heparin, carbamazepine, ceftriaxone, eptifibatide, ibuprofen, trimethoprim-sulfamethoxazole, vancomycin, and mirtazapine could induce drug-induced immune thrombocytopenia (DITP) which could be mild (majorly) or sever. Indeed, there are

several mechanisms utilized by drugs to promote the destruction or depletion of platelets (33, 34), most important of which are the direct bone marrow suppression induced by some drugs and the emergence of drug-dependent antibodies which can activate platelets and consequently, lead to platelet depletion (35). The diagnosis of DITP has always been a challenging issue as some tests are unreliable to detect the causative drugs or pathologic antibodies (36). Moreover, these methods could be time-consuming, expensive, and dependent on specific lab facilities (37). With this regard, machine learning systems have been demonstrated to facilitate the diagnosis of DITP with cost-effective approaches.

Before predicting the DITP diagnosis in patients receiving drugs, it could be important to predict which drug has the potential to induce thrombocytopenia. In this regard, a study investigated the molecular structure of drugs in order to classify them as thrombocytopenia inducers and non-inducers based on their potency to promote antibody production. They utilized seven machine learning models including naive Bayes (NB), support vector machine (SVM), artificial neural network (ANN), k-nearest neighbor (k-NN), adaptive boosting (AdaBoost), eXtreme Gradient Boosting (XGBoost), and random forest (RF) in order to develop binary classification models for the detection of DITP. Among all models, k-NN showed the best performance with 0.62, 62.7%, 69%, and 56.6% AUC, accuracy, sensitivity, and specificity, respectively (38). The results of this study not only exhibited that k-NN outperformed other machine learning models but also implied that the potency of drugs to induce thrombocytopenia could be predicted.

Concerning the DITP, it has been demonstrated that almost 1-3% of patients who received heparin as a medication exhibit thrombocytopenia associated with heparin (39, 40). American Society of Hematology recommended some diagnostic algorithms which could have some demerits, one of the important of which is the limited scope of diagnostic information that is utilized in binary form only (41). However, machine learning algorithms are able to analyze more diverse data in order to develop a more accurate diagnostic system. In this regard, a recent study evaluated 1393 patients for their laboratory and clinical data such as demographics, prothrombin time, and anti-thrombotic therapies. Indeed, they investigated some predictor variables like the degree of thrombocytopenia, timing of thrombocytopenia, the levels of heparin antibodies (assessed by immunoassays), and laboratory data (like CBC). By considering heparin-induced platelet activation assay as the standard, they demonstrated that several clinical hallmarks including degree of thrombocytopenia, timing of thrombocytopenia, WBC and platelet count, and the levels of heparin IgG assessed by chemiluminescent immunoassay (CLIA), ELISA, and particle–gel immunoassay (PaGIA) could be the significant predictors. According to the analyses performed by five machine learning systems including gradient boosting machine, logarithmic regression, elastic net logarithmic regression, SVM, and RF, the best machine learning model was the SVM concerning CLIA and ELISA (with the area under the receiver operating curve [AUC] of 0.98), and the gradient boosting machine in PaGIA (with AUC of 0.99). Indeed, they demonstrated that their developed algorithm was able to dramatically reduce the number of false-negative and false-positive heparin-induced thrombocytopenia cases (42).

A myriad of studies has exhibited the roles of linezolid, a synthetic oxazolidinone antimicrobial

agent, in inducing thrombocytopenia (43, 44). A study utilized a machine learning classification tree model to estimate linezolid-induced thrombocytopenia based on given data including the concentration of linezolid, baseline platelet count, alteration in platelet count (24, 48, 72, 96, and 120 h), creatinine clearance, and body weight. Based on the outcomes, the model utilized platelet count at 96 h and other predictors exhibited better performance among others. They demonstrated that possessing a linezolid total concentration higher than 13.5 or a reduction in platelet count to less than 2.3% at 96 h can display a high risk for linezolid-related thrombocytopenia by day 14. Moreover, the sensitivity and specificity of the model were determined as 92.2 and 78.3%, respectively (45). According to data from 46,520 patients admitted to the intensive care unit (ICU), 3200 met the criteria and were included in a study evaluating the linezolid-related thrombocytopenia by considering a 50% drop in platelet count from the basic levels as the standard for thrombocytopenia. They showed that machine learning was able to predict thrombocytopenia based on routine clinical data with 0.75 accuracy. Besides, the AUC, sensitivity, and specificity were 0.8, 0.78, and 0.62, respectively It is worth mentioning that in this study, the researchers inserted the data of liver and kidney functions into the machine learning model, as this data is essential for the prediction of thrombocytopenia associated with linezolid (46).

3.2. Sepsis-dependent thrombocytopenia

Sepsis is a severe condition caused by infections that could be life-threatening by inducing organ dysfunction and failure (47). It has been reported that the prevalence rate of thrombocytopenia in patients with sepsis hospitalized in the ICU is 50% (48). Two main reasons behind sepsis-associated thrombocytopenia (SAT) are the reduced production of platelet due to bone marrow suppression as well as the elevation of platelet consumption because of inflammatory responses and disseminated intravascular coagulation (DIC). The emergence of thrombocytopenia in sepsis patients is associated with poor prognosis and survival; therefore, the accurate and timely diagnosis of sepsis could be vital for patients (49). Although thrombocytopenia has been reported to be a part of the Sepsis-related Organ Failure Assessment (SOFA) and a great predictor of poor prognosis, it has not been involved enough in studies regarding the application of AI in the estimation of poor prognosis of the ICU hospitalized patients (11). However, there have been some studies evaluating the effects of AI systems in the diagnosis of thrombocytopenia in sepsis patients.

Accordingly, studies focus on analyzing the alterations in the platelet count by machine learning systems. A study utilized four machine learning models NB, ANN, gradient boosting machine, and RF to evaluate thrombocytopenia and other variables of 1455 patients with sepsis in the ICU. According to the results, ANN and gradient boosting machine exhibited the best performance to predict thrombocytopenia with AUC of 73 and 72%, and accuracy of 0.68 and 0.71, respectively. Concerning the prediction of severe thrombocytopenia, all models yielded better outcomes which among them, NB showed the best performance with 77% AUC (50).

Another study evaluated the prognosis of sepsis patients with thrombocytopenia by analyzing the red cell distribution width (RDW) factor using a machine learning system. Indeed, researchers inserted several variables such as CBC, prothrombin time (PT), partial thromboplastin time (PTT), and RDW as well to the XGBoost algorithm in order to predict the 28-day mortality risk. They demonstrated that the SOFA score was the most

significant predictor of mortality and after that, RDW showed the best result. The AUC analysis of subgroups of patients with thrombocytopenia showed that RDW was the most important predictor of mortality with 70 and 57% sensitivity and specificity, respectively. It was shown that RDW was significantly elevated in non-survivors (higher than 16.05) according to logistic regression (51). As RDW has been shown to be a potent indicator of poor prognosis in several cardiovascular diseases and cancers (52, 53) and actually RDW could be associated with inflammation in sepsis patients (54, 55), it is reasonable that RDW could be a proper predictor of mortality risk in sepsis patients with thrombocytopenia.

3.3. Immune thrombocytopenia

Being an autoimmune disorder, immune thrombocytopenic purpura (ITP) is caused by the presence of autoantibodies against platelets. It has been exhibited that IgG autoantibodies could be activated against glycoproteins IIb-IIIa of platelets and target them, leading to ITP (56). Although its prognosis is good in children, ITP could be chronic and associated with mortality in adults (57). A study compared the complications of ITP in children and adults. In this regard, the rate of bleeding reports was similar in both children and adults; however, the rate of comorbidity was remarkably higher in adults (30%) compared with children (3.9%) (58). As stated, ITP not only affects adults but also could influence children. In a study of children diagnosed with ITP, the therapeutic approach using IVIG showed significantly higher response rate compared with anti-D therapy (98% versus 76%, respectively) (59). According to a recent survey in Iran concerning 114 patients (including children) with ITP, fatigue and anxiety around stable platelet counts were the most common reported symptoms (60). An interesting study evaluated the presence of primary antibody deficiency in patients suffer from ITP and showed that 39% of cases had antibody mediated immune deficiency (61).

In a study, some clinical, laboratory, and demographic parameters like age, gender, race, history of ITP, CBC, and antibody levels, were included in five machine learning models RF, SVM, NB, logistic regression, and AdaBoost in order to predict the immune thrombocytopenia in 696 pediatric patients. They showed that the most important predictors of immune thrombocytopenia were the history of primary ITP, mean platelet volume, immature platelet fraction, absolute lymphocyte count, and anti-nuclear antibody level. The 100 tree RF showed the best performance with 0.73 accuracy and 0.79 AUC and in the following, NB demonstrated good outcomes with 0.69 accuracy and 0.79 AUC. All in all, these results implied that the prediction of chronic ITP development in pediatric patients could be carried out with favorable accuracy via AI systems; particularly, the RF model (62).

Another study developed some machine learning models and evaluated them as predictors of life-threatening bleeding in patients with ITP. They utilized some data such as age, onset of ITP and its type, platelet count, uncontrolled diabetes, and cardiovascular disease to train models and develop them. Among all models, RF showed the best efficacy in the prediction of critical bleeding of ITP patients with an AUC of 0.9 in the externally validated experiment and 0.77 in a prospective cohort of 37 centers in China (63). The presence of intracranial hemorrhage as severe bleeding in ITP patients has been shown to be an indication of poor prognosis of the disease. With this regard, in a study, 10 machine learning models were developed to predict 30-day mortality in ITP patients with

intracranial hemorrhage. Indeed, they used multi-center training to train models which was an important event as it could facilitate the way for models to learn patterns and associations among different settings. The most important parameters for the prediction were the count of platelet at the time of intracranial hemorrhage, the coexistence of severe infection, the history of severe bleeding, and the absence of head trauma. According to the internal and independent external validations, the SVM model demonstrated the best performance among the others with an AUC of 0.87 and sensitivity of 0.6 to predict the mortality of ITP patients with intracranial hemorrhage (64).

3.4. Disseminated intravascular coagulation (DIC)

DIC is a severe secondary clinical condition from a variety of diseases and complications such as severe trauma, sepsis, progressed cancer, liver diseases, and obstetric diseases (65). According to the International Society on Thrombosis and Haemostasis (ISTH), DIC is a life-threatening acquired syndrome defined as the activation of intravascular coagulation. The gold standard criteria to diagnose DIC is based on laboratory data including platelet count, fibrinogen, PT, and fibrin-related parameters like D-dimer (66). Therefore, thrombocytopenia could be a sign or a clue for DIC. Rather than ISTH which has been widely utilized, there are other scoring systems such as Japanese Ministry of Health and Welfare (JMHW) and Japanese Association for Acute Medicine (JAAM), both of which could have merits and demerits (67). Nonetheless, there is not a single clinical or laboratory examination with satisfactory sensitivity and specificity in order to diagnose the DIC (68). Accordingly, studies have utilized AI models in order to predict DIC by optimizing the utilization of clinical parameters for the diagnosis of DIC.

In a study, after evaluating several machine learning models, the researchers decided to use ANN as the best AI model to diagnose DIC by analyzing 32 clinical and laboratory variables. The most important predictive factors were the count of platelets, alterations of platelets, D-dimer, and fibrin degradation product (FDP), respectively. In this regard, platelet count and alteration showed the most important role in the prediction of DIC. They reported that ANN exhibited the best scores with an AUC of 0.98, sensitivity of 89.9%, and specificity of 96% (69). Another study evaluated the capacity of three deep learning models XGBoost, long short-term memory neural network, and convolutional neural network (CNN) to predict the risk of DIC in patients hospitalized in the ICU based on given clinical data. Based on the outcomes, researchers showed that creatine kinase (CK), glucose, aspartate aminotransferase (AST), and nucleated red blood cells (NRBC) rate were the most predictable variants regarding DIC. They also demonstrated that CNN outperformed the other two models with an AUC of 0.98 and accuracy of 95.7% and XGBoost showed the worst performance with 0.85 AUC and 82.03% accuracy (70). Another study assessed the risk of DIC after allogeneic hematopoietic stem cell transplantation and developed machine learning models to predict the occurrence of DIC. After analyzing with Lasso regression, the most important variables as DIC risk factors were PT, shock, C-reactive protein (CRP), internal normalized ratio (INR), bacterial infection, oxygenation, and fibrinogen, respectively. Besides, they evaluated five machine learning models XGBoost, logistic regression, AdaBoost, RF, and multilayer perceptron (MLP), and found that XGBoost showed the best performance in the prediction the risk of DIC with 0.86 AUC (71).

4. The application of AI in thrombocythemia

If the platelet count exceeds the normal range due to the presence of a defect in the bone marrow, thrombocythemia occurs. If the cause is an unknown factor, the term thrombocythemia could be utilized and if the reason of platelet over-production is known, the term thrombocytosis could be a better option. As stated, thrombocytosis could be due to a reactive event like another condition or disease (secondary thrombocytosis) or a disorder in the bone marrow like myeloproliferative diseases (essential thrombocythemia). Obviously, leaving thrombocytosis untreated could lead to serious life-threatening conditions majorly derived from blood clots causing stroke, pulmonary embolism, transient ischemic attacks, venous thromboembolism (VTE), or in some cases, it could end in myelodysplastic syndrome or induced acute myeloid leukemia (72). Generally, thrombocytosis isn't accompanied by symptoms, and most of its cases are diagnosed during a routine blood test (CBC). With this regard, having more than 450,000 platelet/μL could be diagnosed with thrombocytosis (73). When it comes to AI, researchers have tried to develop AI-based algorithms in order to predict thrombocytosis in vulnerable cases.

Deep venous thrombosis (DVT) is the major cause of cardiovascular diseases and is responsible for a sizable number of morbidity and mortality (74). The precise diagnosis of DVT needs invasive and high-cost methods. There are two clinical criteria in order to categorize DVT risks including the Wells Criteria for evaluating VTE risk in thrombosis-suspected patients (75) and the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score for assessing VTE risk between hospitalized patients (76). Due to the low efficacy of utilized DVT scores in stratifying hospitalized patients (77), the occurrence of DVT has been assessed by AI-based systems in recent articles.

A study used the XGBoost model to predict the development of DVT 12 hours and 24 hours in advance. They investigated 99237 hospitalized patients in both general wards and ICU and showed that the machine learning model was able to predict DVT of patients with 0.83 and 0.85 AUC at 12- and 24-hour windows, respectively. Besides, the most important predictors of DVT were cancer history, VTE history, and INR, in order. These results could pave the way for early detection of DVT and optimizing the prophylactic anticoagulants; consequently, reducing the occurrence of pulmonary emboli (78). In another study, three machine learning models SVM, RF, and logistic multivariable analysis were used to evaluate 318 essential thrombocythemia patients with a history of thrombosis. By analyzing biomarkers, machine learning demonstrated the most important independent predictors of thrombosis, cardiovascular risk factor, and RDW standard deviation (SD) (79). The details of studies using machine learning systems regarding platelet disorders were provided in **Table 1**. Moreover, **Figure 2** displayed a comparison between machine learning models with the best performances.

5. Conclusion and future prospects

Artificial intelligence (AI) systems hold immense potential in the context of platelet disorders, offering opportunities to enhance the diagnosis and treatment actions. With this regard, AI algorithms have shown the capacity to learn patterns and analyze relationships in order to find the most important variable and predict the occurrence of platelet disorders. The typical diagnostic tools regarding platelet disorders could be invasive, time-consuming, and costly; yet, the application of

machine learning models has revolutionized the early diagnosis of platelet disorders in order to take action in critical situations. However, there are still a few numbers of machine learning-driven approaches regarding platelet disorders, most of which were associated with thrombocytopenia. Indeed, studies majorly focus on the role of machine learning models in the context of thrombocytopenia disorders including DITP, SAT, ITP, and DIC.

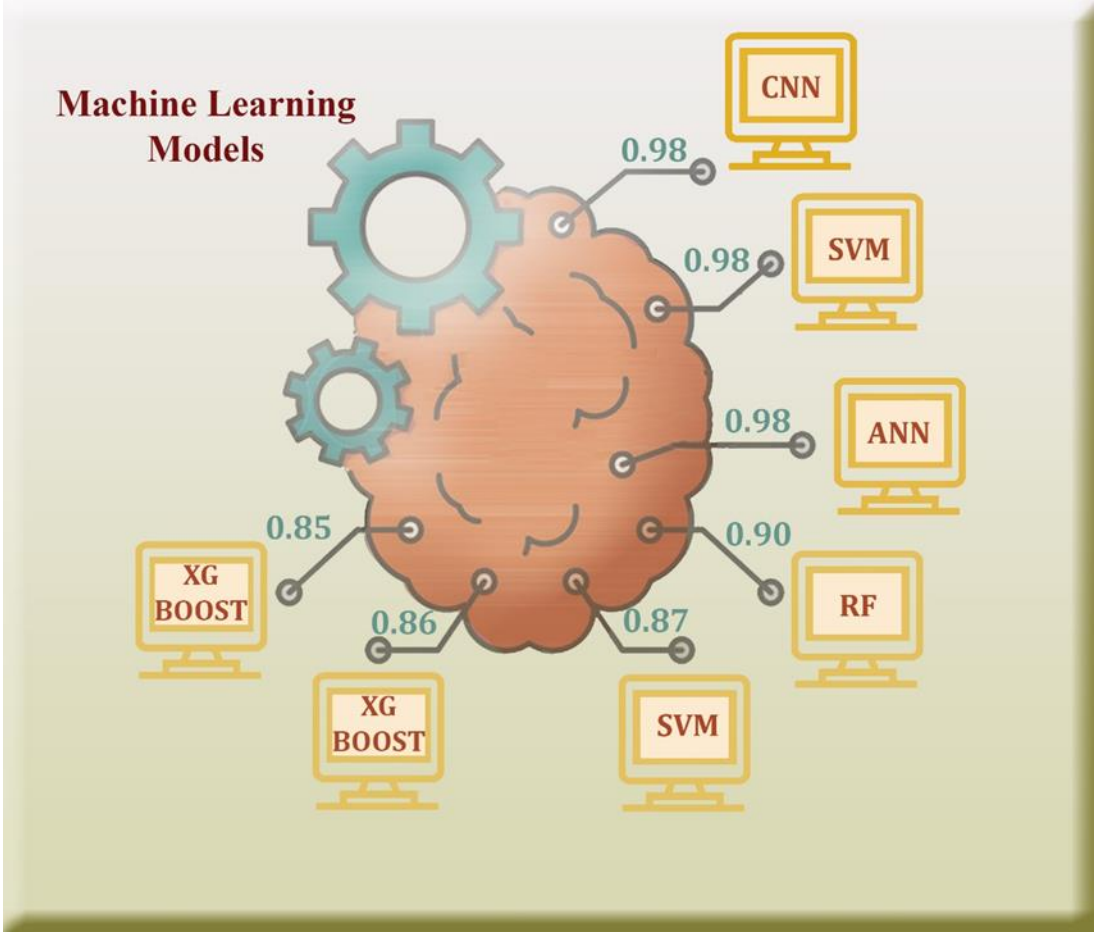

Figure 2. **Comparison of machine learning models.** We analyzed the data of studies that utilized machine learning models in order to predict platelet disorders. According to the area under the receiver operating curve (AUC) (a minimum of 0.85), three studies using SVM, ANN, and CNN models exhibited the best performance with an AUC of 0.98. In the following, RF and SVM showed 0.9 and 0.87 AUC, respectively in two other studies. Moreover, two studies utilizing XGBoost as the machine learning model exhibited AUCs of 0.86 and 0.85 which are satisfactory. Our investigation showed that the most frequently used variables are age, gender, history of diseases, CBC, MCV, MCH, MCHC, PT, PTT, D-dimer, creatinine, and INR. It is worth mentioning that those studies demonstrating the best AUC (0.98) used a sizable number of demographics, clinical, and laboratory parameters while the others utilized a way lower number of parameters. Interestingly, among the best models, only SVM showed the best capacity with a relatively lower number of included variables implying the efficacy of SVM in predicting platelet disorders.

Regarding thrombocythemia, researchers utilized machine learning systems to predict the development of thrombosis before its onset. It could be crucial to estimate if susceptible patients can develop thrombosis like DVT or not in order to save lives. Nevertheless, this area requires further investigation in order to reach the most precise method.

Table 1. **Details of imported clinical data and efficacy of machine learning models in platelet disorders.**

Ref	Parameters					Model	Efficacy			
	Demographic	Hematology	Coagulation	Biochemistry	Immunology		AUC	Accuracy	Sensitivity	Specificity
DITP										
(38)	NA					K-NN	0.62	62.7%	69%	56.6%
(42)	Ag Ge Hi Th	WBC Plt	PT	CRP	Ab	SVM	0.98	#	96%	95%
(45)	Ag Ge Hi	Plt		Crea OT/PT		Tree	#	#	92.2%	78.3%
(46)	Ag Ge Hi	Plt	INR	Crea OT/PT			0.8	0.75	0.78	0.62
SAT										
(50)	Ag Ge Hi Th Al/Sm	WBC RBC Plt	PT PTT D-di INR	CRP Crea OT/PT Mi		ANN	73%	0.68	#	0.71
(51)	Ag Ge Hi	WBC Plt RDW	PT PTT			XGBoost	#	#	70%	57%
ITP										
(62)	Ag Ge Hi	WBC Plt			Ab	RF	0.79	0.73	#	#
(63)	Ag Hi	Plt				RF	0.9	#	#	#
(64)	Hi	Plt				SVM	0.87	#	0.6	#
DIC										
(69)	Ag Ge Hi	WBC RBC Plt RDW CH/V	PT PTT D-di INR			ANN	0.98		89.9%	96%
(70)	Ag Ge Hi Th	WBC RBC Plt RDW CH/V	PT PTT D-di	CRP Crea OT/PT Mi		CNN	0.98	95.68%	#	#
(71)	Hi	WBC Plt	PT INR	CRP Crea		XGBoost	0.86	#	#	#
Thrombocytosis										
(78)	Ag Ge Hi Th		INR			XGBoost	0.85	#	0.8	0.75

Ag: Age; **Ge:** Gender; **Hi:** History of diseases; **Th:** Therapy; Al/Sm: Alcohol/Smoking; **Ab:** Antibody; **Crea:** Creatinine; **OT/PT:** AST, ALT; **CH/V (Corpuscular Hemoglobin/Volume):** MCV, MCH, MCHC; **D-di:** D-dimer; **Mi:** Minerals

Researchers inserted several demographical, clinical, and laboratory data into models and showed satisfying outcomes in predicting platelet disorders. Generally, the precise accuracy, AUC, sensitivity, and specificity depend on the situation of the examinations such as the utilized algorithm and the condition of the disease. However, by comparing the AUC of models in studies, we exhibited that in three studies, SVM, ANN, and CNN reached the highest efficacy with an AUC of 0.98. Two other studies showed 0.9 and 0.87 AUC for RF and SVM, respectively. Moreover, in two studies, XGBoost demonstrated 0.86 and 0.85 AUC. Taken together, it could be inferred that more data is required in order to interpret and compare the effectiveness of AI models; however, SVM showed the best performance. Furthermore, by evaluating the parameters of those studies, we concluded that studies that included a higher number of parameters reached better performance. To be precise, the more parameter a model takes, the more accurate it could be. Therefore, the better efficacy of models in those studies could be associated with a high number of parameters they investigated; however, it couldn't be a promising aspect because it would be time-consuming and costly to include a sizable number of parameters for models. Accordingly, SVM again exhibited better performance for the relatively lower number of parameters it utilized and the higher AUC it achieved. Regarding the analyzed parameters, we concluded the most important variables helping the prediction of platelet disorders are the history of the disease, platelet counts, and coagulation factors.

It is worth mentioning that by analyzing the patterns, models not only predict the risk of platelet disorders but also estimate the rate of mortality and or the occurrence of specific complications. Moreover, studies have shown which parameters and biomarkers could have the most potency to predict. This could be useful for physicians to evaluate those meaningful parameters primarily and for researchers to consider them as important predictive variations in AI studies. Although these studies exhibited promising outcomes, the application of AI systems in the diagnosis and treatment of platelet disorders needs additional evaluation. Advancements in AI technology could lead to the development of more accurate and efficient diagnostic tools, predictive models, and personalized treatment strategies.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Harrison P. Platelet function analysis. Blood reviews. 2005;19(2):111-23.

2. Noetzli LJ, French SL, Machlus KR. New insights into the differentiation of megakaryocytes from hematopoietic progenitors. Arteriosclerosis, thrombosis, and vascular biology. 2019;39(7):1288-300.

3. Haley KM. Platelet Disorders. Pediatr Rev. 2020;41(5):224-35.

4. Lee E-J, Lee AI. Thrombocytopenia. Primary Care: Clinics in Office Practice. 2016;43(4):543-57.

5. Bashash D, Hosseini-Baharanchi FS, Rezaie-Tavirani M, Safa M, Akbari Dilmaghani N, Faranoush M, Abolghasemi H. The Prognostic Value of Thrombocytopenia in COVID-19 Patients; a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2020;8(1):e75.

6. Delshad M, Safaroghli-Azar A, Pourbagheri-Sigaroodi A, Poopak B, Shokouhi S, Bashash D. Platelets in the perspective of COVID-19; pathophysiology of thrombocytopenia and its implication as prognostic and therapeutic opportunity. Int Immunopharmacol. 2021;99:107995.

7. Vannucchi AM, Barbui T. Thrombocytosis and thrombosis. ASH Education program book. 2007;2007(1):363-70.

8. Mohan G, Malayala SV, Mehta P, Balla M. A comprehensive review of congenital platelet disorders, thrombocytopenias and thrombocytopathies. Cureus. 2020;12(10).

9. Al-Huniti A, Kahr WH. Inherited platelet disorders: diagnosis and management. Transfusion Medicine Reviews. 2020;34(4):277-85.

10.Cheng Y, Chen C, Yang J, Yang H, Fu M, Zhong X, Wang B, He M, Hu Z, Zhang Z. Using Machine Learning Algorithms to Predict Hospital Acquired Thrombocytopenia after Operation in the Intensive Care Unit: A Retrospective Cohort Study. Diagnostics. 2021;11(9):1614.

11.Elshoeibi AM, Ferih K, Elsabagh AA, Elsayed B, Elhadary M, Marashi M, Wali Y, Al-Rasheed M, Al-Khabori M, Osman H, Yassin M. Applications of Artificial Intelligence in Thrombocytopenia. Diagnostics (Basel). 2023;13(6).

12.Janiesch C, Zschech P, Heinrich K. Machine learning and deep learning. Electronic Markets. 2021;31(3):685-95.

13.Singh M, Pujar GV, Kumar SA, Bhagyalalitha M, Akshatha HS, Abuhaija B, Alsoud AR, Abualigah L, Beeraka NM, Gandomi AH. Evolution of machine learning in tuberculosis diagnosis: a review of deep learning-based medical applications. Electronics. 2022;11(17):2634.

14.Wang F, Casalino LP, Khullar D. Deep learning in medicine—promise, progress, and challenges. JAMA internal medicine. 2019;179(3):293-4.

15.Mani V, Ghonge MM, Chaitanya NK, Pal O, Sharma M, Mohan S, Ahmadian A. A new blockchain and fog computing model for blood pressure medical sensor data storage. Computers and Electrical Engineering. 2022;102:108202.

16.Liu P-r, Lu L, Zhang J-y, Huo T-t, Liu S-x, Ye Z-w. Application of artificial intelligence in medicine: an overview. Current Medical Science. 2021;41(6):1105-15.

17.Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. Journal of family medicine and primary care. 2019;8(7):2328.

18.Mitsala A, Tsalikidis C, Pitiakoudis M, Simopoulos C, Tsaroucha AK. Artificial Intelligence in Colorectal Cancer Screening, Diagnosis and Treatment. A New Era. Curr Oncol. 2021;28(3):1581-607.

19.Pei Q, Luo Y, Chen Y, Li J, Xie D, Ye T. Artificial intelligence in clinical applications for lung cancer: diagnosis, treatment and prognosis. Clin Chem Lab Med. 2022;60(12):1974-83.

20.Huang S, Yang J, Fong S, Zhao Q. Artificial intelligence in the diagnosis of COVID-19: challenges and perspectives. Int J Biol Sci. 2021;17(6):1581-7.

21.Huang X, Wang H, She C, Feng J, Liu X, Hu X, Chen L, Tao Y. Artificial intelligence promotes the diagnosis and screening of diabetic retinopathy. Front Endocrinol (Lausanne). 2022;13:946915.

22.Nomura A, Noguchi M, Kometani M, Furukawa K, Yoneda T. Artificial Intelligence in Current Diabetes Management and Prediction. Curr Diab Rep. 2021;21(12):61.

23. Nahar JK, Lopez-Jimenez F. Utilizing Conversational Artificial Intelligence, Voice, and Phonocardiography Analytics in Heart Failure Care. Heart Fail Clin. 2022;18(2):311-23.
24. Tian Y, Yang J, Lan M, Zou T. Construction and analysis of a joint diagnosis model of random forest and artificial neural network for heart failure. Aging (Albany NY). 2020;12(24):26221-35.
25. Yasmin F, Shah SMI, Naeem A, Shujauddin SM, Jabeen A, Kazmi S, Siddiqui SA, Kumar P, Salman S, Hassan SA, Dasari C, Choudhry AS, Mustafa A, Chawla S, Lak HM. Artificial intelligence in the diagnosis and detection of heart failure: the past, present, and future. Rev Cardiovasc Med. 2021;22(4):1095-113.
26. Gedefaw L, Liu CF, Ip RKL, Tse HF, Yeung MHY, Yip SP, Huang CL. Artificial Intelligence-Assisted Diagnostic Cytology and Genomic Testing for Hematologic Disorders. Cells. 2023;12(13).
27. Cai S, Han IC, Scott AW. Artificial intelligence for improving sickle cell retinopathy diagnosis and management. Eye (Lond). 2021;35(10):2675-84.
28. El Alaoui Y, Elomri A, Qaraqe M, Padmanabhan R, Yasin Taha R, El Omri H, El Omri A, Aboumarzouk O. A Review of Artificial Intelligence Applications in Hematology Management: Current Practices and Future Prospects. J Med Internet Res. 2022;24(7):e36490.
29.Radakovich N, Cortese M, Nazha A. Acute myeloid leukemia and artificial intelligence, algorithms and new scores. Best Pract Res Clin Haematol. 2020;33(3):101192.
30. Belcic T, Cernelc P, Sever M. PB2225 Artificial intelligence aiding in diagnosis of JAK2 V617F negative patients with WHO defined essential thrombocythemia. HemaSphere. 2019;3(S1):998.
31.Greenberg EM, Kaled ES. Thrombocytopenia. Crit Care Nurs Clin North Am. 2013;25(4):427-34, v.
32. Smock KJ, Perkins SL. Thrombocytopenia: an update. Int J Lab Hematol. 2014;36(3):269-78.
33. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7(6):911-8.
34. Curtis BR. Drug-induced immune thrombocytopenia: incidence, clinical features, laboratory testing, and pathogenic mechanisms. Immunohematology. 2014;30(2):55-65.
35. Vayne C, Guéry EA, Rollin J, Baglo T, Petermann R, Gruel Y. Pathophysiology and Diagnosis of Drug-Induced Immune Thrombocytopenia. J Clin Med. 2020;9(7).
36. Arnold DM, Curtis BR, Bakchoul T. Recommendations for standardization of laboratory testing for drug-induced immune thrombocytopenia: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(4):676-8.
37. Arnold DM, Kukaswadia S, Nazi I, Esmail A, Dewar L, Smith JW, Warkentin TE, Kelton JG. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. J Thromb Haemost. 2013;11(1):169-76.
38. Wang B, Tan X, Guo J, Xiao T, Jiao Y, Zhao J, Wu J, Wang Y. Drug-Induced Immune Thrombocytopenia Toxicity Prediction Based on Machine Learning. Pharmaceutics. 2022;14(5).
39. Hogan M, Berger JS. Heparin-induced thrombocytopenia (HIT): Review of incidence, diagnosis, and management. Vasc Med. 2020;25(2):160-73.
40. Dhakal B, Kreuziger LB, Rein L, Kleman A, Fraser R, Aster RH, Hari P, Padmanabhan A. Disease burden, complication rates, and health-care costs of heparin-induced thrombocytopenia in the USA: a population-based study. Lancet Haematol. 2018;5(5):e220-e31.

41. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, Linkins LA, Rodner SB, Selleng S, Warkentin TE, Wex A, Mustafa RA, Morgan RL, Santesso N. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22):3360-92.

42. Nilius H, Cuker A, Haug S, Nakas C, Studt JD, Tsakiris DA, Greinacher A, Mendez A, Schmidt A, Wuillemin WA, Gerber B, Kremer Hovinga JA, Vishnu P, Graf L, Kashev A, Sznitman R, Bakchoul T, Nagler M. A machine-learning model for reducing misdiagnosis in heparin-induced thrombocytopenia: A prospective, multicenter, observational study. EClinicalMedicine. 2023;55:101745.

43. Natsumoto B, Yokota K, Omata F, Furukawa K. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014;42(6):1007-12.

44. Tajima M, Kato Y, Matsumoto J, Hirosawa I, Suzuki M, Takashio Y, Yamamoto M, Nishi Y, Yamada H. Linezolid-Induced Thrombocytopenia Is Caused by Suppression of Platelet Production via Phosphorylation of Myosin Light Chain 2. Biol Pharm Bull. 2016;39(11):1846-51.

45. Takahashi S, Tsuji Y, Kasai H, Ogami C, Kawasuji H, Yamamoto Y, To H. Classification Tree Analysis Based On Machine Learning for Predicting Linezolid-Induced Thrombocytopenia. J Pharm Sci. 2021;110(5):2295-300.

46. Maray I, Rodríguez-Ferreras A, Álvarez-Asteinza C, Alaguero-Calero M, Valledor P, Fernández J. Linezolid induced thrombocytopenia in critically ill patients: Risk factors and development of a machine learning-based prediction model. J Infect Chemother. 2022;28(9):1249-54.

47. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016;315(8):801-10.

48. Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, Bobbaers H. Thrombocytopenia and prognosis in intensive care. Crit Care Med. 2000;28(6):1871-6.

49. Larkin CM, Santos-Martinez M-J, Ryan T, Radomski MW. Sepsis-associated thrombocytopenia. Thrombosis research. 2016;141:11-6.

50. Jiang X, Wang Y, Pan Y, Zhang W. Prediction Models for Sepsis-Associated Thrombocytopenia Risk in Intensive Care Units Based on a Machine Learning Algorithm. Front Med (Lausanne). 2022;9:837382.

51. Ling J, Liao T, Wu Y, Wang Z, Jin H, Lu F, Fang M. Predictive value of red blood cell distribution width in septic shock patients with thrombocytopenia: A retrospective study using machine learning. J Clin Lab Anal. 2021;35(12):e24053.

52. Liu S, Wang P, Shen PP, Zhou JH. Predictive Values of Red Blood Cell Distribution Width in Assessing Severity of Chronic Heart Failure. Med Sci Monit. 2016;22:2119-25.

53. Ellingsen TS, Lappegård J, Skjelbakken T, Braekkan SK, Hansen JB. Impact of red cell distribution width on future risk of cancer and all-cause mortality among cancer patients - the Tromsø Study. Haematologica. 2015;100(10):e387-9.

54. Wang AY, Ma HP, Kao WF, Tsai SH, Chang CK. Red blood cell distribution width is associated

with mortality in elderly patients with sepsis. Am J Emerg Med. 2018;36(6):949-53.
55. Jandial A, Kumar S, Bhalla A, Sharma N, Varma N, Varma S. Elevated Red Cell Distribution Width as a Prognostic Marker in Severe Sepsis: A Prospective Observational Study. Indian J Crit Care Med. 2017;21(9):552-62.
56. Zainal A, Salama A, Alweis R. Immune thrombocytopenic purpura. J Community Hosp Intern Med Perspect. 2019;9(1):59-61.
57. Swinkels M, Rijkers M, Voorberg J, Vidarsson G, Leebeek FWG, Jansen AJG. Emerging Concepts in Immune Thrombocytopenia. Front Immunol. 2018;9:880.
58. Kühne T, Berchtold W, Michaels LA, Wu R, Donato H, Espina B, Tamary H, Rodeghiero F, Chitlur M, Rischewski J. Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. Haematologica. 2011;96(12):1831.
59. Shahgholi E, Vosough P, Sotoudeh K, Arjomandi K, Ansari S, Salehi S, Faranoush M, Ehsani MA. Intravenous immune globulin versus intravenous anti-D immune globulin for the treatment of acute immune thrombocytopenic purpura. The Indian Journal of Pediatrics. 2008;75:1231-5.
60. Eshghi P, Abolghasemi H, Akhlaghi AA, Ashrafi F, Bordbar M, Hajifathali A, Hosseini H, Mirbehbahani N, Abedini A, Shahsavarani N. Patient and Physician Perspectives in the Management of Immune Thrombocytopenia in Iran: Responses from the ITP World Impact Survey (I-WISh). Clinical and Applied Thrombosis/Hemostasis.
2023;29:10760296221130335.
61. Rahiminejad MS, Sadeghi MM, Mohammadinejad P, Sadeghi B, Abolhassani H, Firoozabadi MMD, Fathi SM, Rezvani H, Bahoush G, Ehsani MA. Evaluation of humoral immune function in patients with chronic idiopathic thrombocytopenic purpura. Iranian Journal of Allergy, Asthma and Immunology. 2013:50-6.
62.Kim TO, MacMath D, Pettit RW, Kirk SE, Grimes AB, Gilbert MM, Powers JM, Despotovic JM. Predicting Chronic Immune Thrombocytopenia in Pediatric Patients at Disease Presentation: Leveraging Clinical and Laboratory Characteristics Via Machine Learning Models. Blood. 2021;138:1023.
63.An Z-Y, Wu Y-J, Huang R-B, Zhou H, Huang Q-S, Fu H-X, Jiang Q, Jiang H, Lu J, Huang X-J. P1655: PERSONALIZED MACHINE-LEARNING-BASED PREDICTION FOR CRITICAL IMMUNE THROMBOCYTOPENIA BLEEDS: A NATIONWIDE DATA STUDY. HemaSphere. 2022;6(Suppl).
64.Zhang X-H, Huang R-B, Zhang J-N, Huang Q-S, Fu H-X. P1652: MACHINE-LEARNING-BASED MORTALITY PREDICTION OF ICH IN ADULTS WITH ITP: A NATIONWIDE REPRESENTATIVE MULTICENTRE STUDY. HemaSphere. 2022;6(Suppl).
65.Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev Dis Primers. 2016;2:16037.
66.Taylor FB, Jr., Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327-30.
67.Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, Koseki K, Mayumi T, Murata A, Ikeda T, Ishikura H, Ueyama M, Ogura H, Kushimoto S, Saitoh D, Endo S, Shimazaki S. A multicenter,

prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med. 2006;34(3):625-31.

68.Levi M. Diagnosis and treatment of disseminated intravascular coagulation. Int J Lab Hematol. 2014;36(3):228-36.

69.Yoon JG, Heo J, Kim M, Park YJ, Choi MH, Song J, Wyi K, Kim H, Duchenne O, Eom S, Tsoy Y. Machine learning-based diagnosis for disseminated intravascular coagulation (DIC): Development, external validation, and comparison to scoring systems. PLoS One. 2018;13(5):e0195861.

70.Yang H, Li J, Liu S, Zhang M, Liu J. An interpretable DIC risk prediction model based on convolutional neural networks with time series data. BMC Bioinformatics. 2022;23(1):471.

71.An Z-Y, Wu Y-J, He Y, Zhu X-L, Su Y, Wang C-C, Han T-X, Fu H-X, Wang F-R, Mo X-D. Machine-Learning Based Early Warning System for Prediction for Disseminated Intravascular Coagulation after Allogeneic Hematopoietic Stem Cell Transplantation: A Nationwide Multicenter Study. Blood. 2021;138(Supplement 1):2113-.

72.Schafer AI. Thrombocytosis. New England Journal of Medicine. 2004;350(12):1211-9.

73.Stockklausner C, Duffert CM, Cario H, Knöfler R, Streif W, Kulozik AE. Thrombocytosis in children and adolescents-classification, diagnostic approach, and clinical management. Ann Hematol. 2021;100(7):1647-65.

74.Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: a United States cost model for a preventable and costly adverse event. Thromb Haemost. 2011;106(3):405-15.

75.Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349(13):1227-35.

76.Spyropoulos AC, Anderson FA, Jr., FitzGerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann JF, Tapson V, Froehlich JB, Monreal M, Merli GJ, Pavanello R, Turpie AGG, Nakamura M, Piovella F, Kakkar AK, Spencer FA. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest. 2011;140(3):706-14.

77.Greene MT, Spyropoulos AC, Chopra V, Grant PJ, Kaatz S, Bernstein SJ, Flanders SA. Validation of Risk Assessment Models of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med. 2016;129(9):1001.e9-.e18.

78.Ryan L, Mataraso S, Siefkas A, Pellegrini E, Barnes G, Green-Saxena A, Hoffman J, Calvert J, Das R. A Machine Learning Approach to Predict Deep Venous Thrombosis Among Hospitalized Patients. Clin Appl Thromb Hemost. 2021;27:1076029621991185.

79.Chen J, Dong H, Fu R, Liu X, Xue F, Liu W, Chen Y, Sun T, Ju M, Dai X. Machine learning analyses constructed a novel model to predict recurrent thrombosis in adults with essential thrombocythemia. Journal of Thrombosis and Thrombolysis. 2023:1-10.