Digital Technologies in Hereditary Coagulation Disorders: A Systematic Review

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Hamostaseologie 2024;44:446–458.

Abstract

Background This systematic review aims to comprehensively survey digital technologies used in the prevention, diagnosis, and treatment of hereditary blood coagulation disorders.

Methods The systematic review was performed according to the PRISMA guidelines. A systematic search was conducted on PubMed on January 29, 2024. Articles were excluded if they were reviews, meta-analyses, or systematic reviews. Articles were included if they were published from January 1, 2014, onward, written in English, described an actual application of digital tools, were in the context of hereditary coagulation disorders, and involved studies or trials on humans or human data with at least three subjects.

Results The initial PubMed search on January 29, 2024, identified 2,843 articles, with 672 from January 1, 2014, onward. After screening, 21 articles met the exclusion and inclusion criteria. Among these, 12 focused on artificial intelligence (AI) technologies and 9 on digital applications. AI was predominantly used for diagnosis (five studies) and treatment (four studies), while digital applications were mainly used for treatment (eight studies). Most studies addressed hemophilia A, with a smaller number including hemophilia B or von Willebrand disease.

Discussion The findings reveal a lack of intervention studies in the prevention, diagnosis, and treatment. However, digital tools, including AI and digital applications, are increasingly used in managing hereditary coagulation disorders. AI enhances diagnostic accuracy and personalizes treatment, while digital applications improve patient care and engagement. Despite these advancements, study biases and design limitations indicate the need for further research to fully harness the potential of these technologies.

Keywords
- coagulation
- digital technologies
- artificial intelligence
- systematic review
- E-diary

Introduction

Hereditary coagulation disorders represent a significant medical challenge due to their complexity and potential severity.[1] These disorders, which include hemophilia A and B, von Willebrand disease, and other less common genetic conditions, affect the blood's ability to clot properly, leading to excessive bleeding, bruising, joint bleeding, and even death.[2–4] Managing the disease progression, as well as

received
August 1, 2024
accepted after revision
September 14, 2024

DOI https://doi.org/10.1055/a-2415-8646.
ISSN 0720-9355.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

preserving the quality of life of patients, requires ongoing monitoring, frequent medical consultations, and adherence to treatment regimens, posing a considerable burden on the patients and the healthcare system alike.[1,3]

Digital technologies have revolutionized various aspects of healthcare, offering new tools and methods to enhance patient care in recent years.[5,6] These innovations encompass various applications, from mobile health apps and telemedicine to artificial intelligence (AI) systems. Some applications provide patients with accessible platforms for tracking their symptoms, managing medications, and communicating with healthcare providers. Others enable remote consultations, reducing the need for frequent in-person visits and making healthcare more accessible, particularly for patients in remote or underserved areas. AI technologies, including machine learning and statistical methods, have the potential to improve diagnostic accuracy, predict bleeding episodes, and personalize treatment plans based on individual patient data.

This systematic review examines how digital technologies are currently used in preventing, diagnosing, and treating hereditary coagulation disorders, aiming to identify common challenges that could be effectively addressed through digital solutions. To our knowledge, no systematic review has been published on integrating digital technologies to manage these disorders. Furthermore, there are no ongoing reviews registered on PROSPERO that focus on digital technologies in this area.

Methods

Search Strategy

A systematic review was conducted according to the PRISMA guidelines.[7] The search strategy was designed to identify relevant articles involving digital tools (search terms: mobile application, artificial intelligence, AI, machine learning, computational intelligence, computer reasoning, computer vision systems, knowledge acquisition, knowledge representation, machine intelligence, transfer learning, telemedicine, mobile health, tele-care, tele-icu, tele-intensive care, tele-referral, telecare, telehealth, virtual medicine, eHealth, and mHealth) in the context of hereditary blood coagulation disorders (search terms: blood coagulation disorders [MeSH term], hemostasis disorder, bleeding disorder). Keywords were expanded based on MeSH synonyms and additional related keywords that are not yet present in the current versions of MeSH (e.g., transfer learning). Review articles or meta-analyses were excluded from the search.

The search term used was:

> ((Blood Coagulation Disorders [MeSH Terms] *or* “hemostasis disorder” *or* “bleeding disorder”) *and* (“mobile application” *or* “artificial intelligence” *or* telemedicine *or* “mobile health” *or* “tele-care” *or* “tele-icu” *or* “tele-intensive care” *or* “tele-referral” *or* telecare *or* telehealth *or* “virtual medicine” *or* eHealth *or* mHealth *or* AI *or* “computational intelligence” *or* “computer reasoning” *or* “computer vision systems” *or* “knowledge acquisition” *or* “knowledge representation” *or* “machine intelligence” *or* “transfer learning” *or* “machine learning”)) *not* (meta-analysis [pt] *or* review [pt] *or* “systematic review” [pt]).

The search was conducted in PubMed on January 29, 2024. We focused on hereditary coagulation disorders, excluding nonhereditary ones to highlight digital tools designed for genetic disorders. This approach provides targeted insights into digital solutions for the lifelong management and treatment of hereditary bleeding disorders. We excluded acquired coagulation disorders, as these are most common in acute and clinical care.

Inclusion and Exclusion Criteria

Initially, a Python script automatically checked all articles ($N = 2{,}843$). The script included all articles published from January 1, 2014, onward and excluded all articles tagged in PubMed with a language other than English. We decided to focus on studies from the last 10 years to ensure our systematic review captures the most relevant and up-to-date studies. This time frame reflects current advancements while avoiding outdated research, providing a manageable and relevant synthesis for contemporary practice.

Next, the titles and abstracts of the remaining articles were manually screened. Articles were excluded if they were reviews, meta-analyses, or systematic reviews (not tagged in PubMed). Articles were included if they met the following criteria: publication year 2014 or newer, written in English, described an actual application of digital tools (e.g., mobile applications, AI, and telemedicine), were in the context of coagulation disorders, used studies or trials on humans or human data with at least three subjects, and focused on hereditary disorders.

Article Selection

The articles ($N = 645$) were divided to ensure a random and balanced assignment, with each article being reviewed by two of the seven reviewers (F.K., M.K., L.N., L.B., M.H., L.M.R., S.M.J.). The reviewers independently screened all titles and abstracts for eligibility based on the inclusion and exclusion criteria. If there was a disagreement between the two reviewers, a third reviewer resolved the conflict by reviewing the title and abstract with the knowledge of the conflict.

Next, full-text articles of potentially eligible studies ($N = 50$) were retrieved and independently screened by two reviewers each. The articles were again divided randomly to maintain equal and balanced assignments by six reviewers (M.K., L.N., L.B., M.H., L.M.R., S.M.J.), with the remaining reviewer (F.K.) screening all the articles. The same inclusion and exclusion criteria used in the initial screening were applied again. Any discrepancies between the two reviewers were discussed and resolved through reexamination and consensus.

Data Extraction

We predefined the extraction structure and iteratively expanded and adjusted it during the extraction process to include additional items as needed. For each of the articles from the final set of included articles ($N = 21$), the two reviewers performing the full-text screening independently extracted data. They extracted information about the study characteristics, participant characteristics, intervention characteristics, digital tool characteristics, and outcome. The extracted information was then compared and discussed between the two reviewers to ensure consistency and accuracy. Any disagreements were resolved through discussion and consensus.

Data Synthesis

The extracted data were synthesized qualitatively and quantitatively, focusing on study characteristics, participant characteristics, kind of intervention, digital tool characteristics, and the outcomes reported in the context of digital tools in hereditary blood coagulation disorders. The results are organized on study focus (prevention/diagnosis/treatment) and digital tool (digital application/AI) to provide a comprehensive overview of the current state of digital tools in this field.

In our definition, statistical models such as logistic regression and random forests were categorized as AI because they are integral components of AI. These models employed data-driven algorithms to analyze and predict outcomes based on datasets, thus enabling decision-making and personalized treatment strategies in medical contexts.

Results

The initial search on PubMed on January 29, 2024, yielded 2,843 articles. Out of them, 645 articles were automatically included because they were published in English and published from January 1, 2014, onward. After applying the remaining inclusion and exclusion criteria by two to three reviewers, 21 articles were included for the final synthesis (►**Fig. 1**).

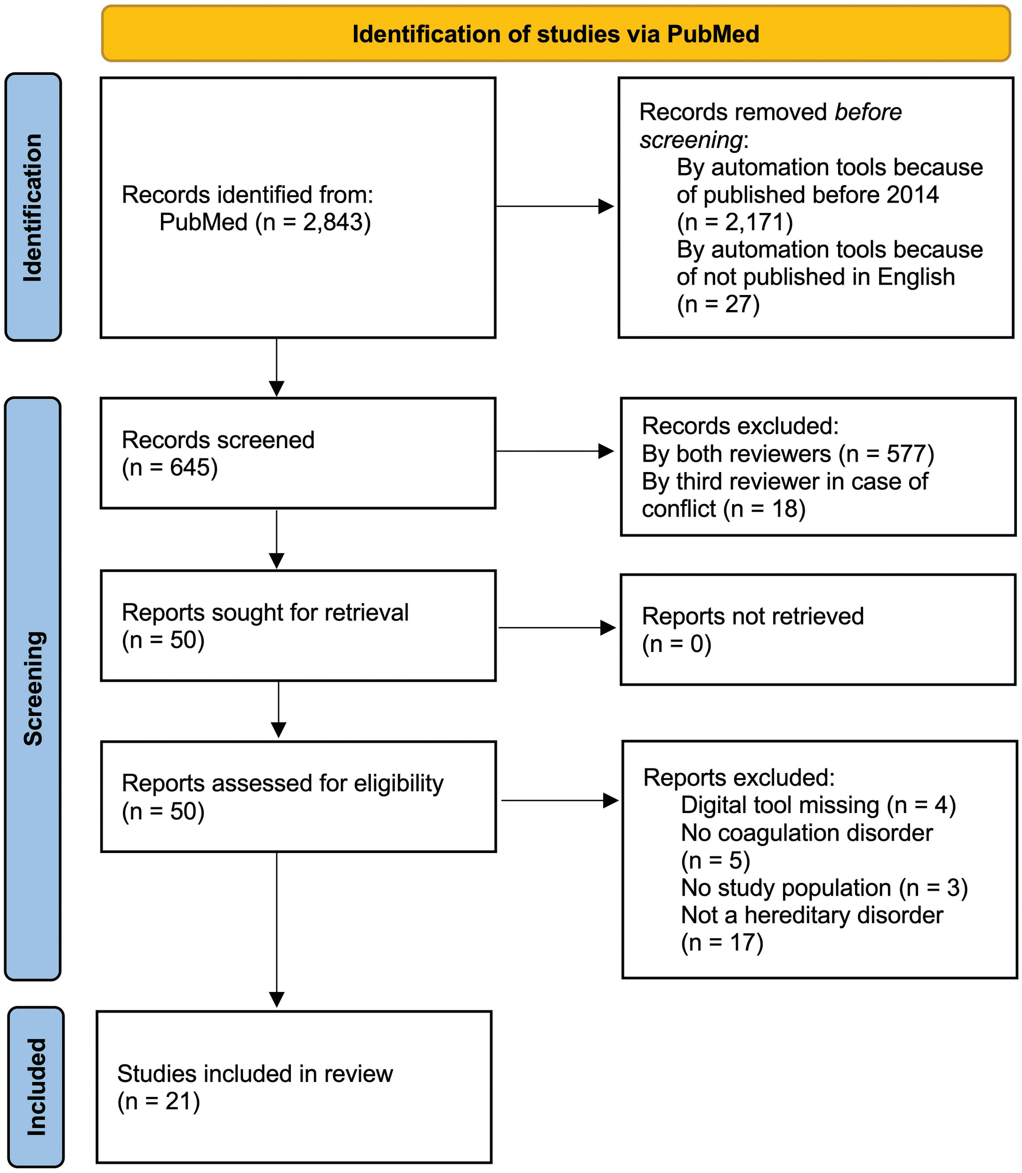

Fig. 1 PRISMA flow diagram of article selection.[7]

Articles that exclusively used digital technologies for calculating ratios, such as the study by Evans et al, which utilized Excel,[8] are excluded from consideration. Articles like Méndez Barrera et al, which predict multiple diseases, including only one coagulation disorder in their 12 investigated disorders,[9] instead of focusing on inherited coagulation disorders as the primary object of investigation are also omitted. Additionally, articles such as Valls et al, which do not center on human data studies or trials but rather on adverse event reports,[10] are excluded.

In terms of the investigated coagulation disorders, 12 studies focus on hemophilia A.[11–22] Three studies address both hemophilia A and B,[23–25] while two studies examine hemophilia A and B as well as von Willebrand disease.[26,27] Three studies focus on general hemophilia,[28–30] and one study concentrates on hemophilic arthropathy.[31]

The frequency of tool usage varied significantly. Among AI tools, statistical methods were the most commonly employed, appearing in 8 out of 21 studies. For digital applications, e-diaries were the most frequent, used in 5 out of 21 studies (see ►Fig. 2).

The 21 articles are split into three tables. ►Table 1 includes four studies on prevention, with three focusing on AI[15–17] and one on digital applications.[30] ►Table 2 presents five studies that discuss diagnosis, all of which focus on AI.[12,14,18,22,31] ►Table 3 lists 12 studies discussing treatment, with four focusing on AI[13,19–21] and eight on digital applications.[11,23–29]

Prevention

Artificial Intelligence

All three AI studies employed statistical methods. van Velzen et al used logistic regression to calculate odds ratios to identify FVIII concentrate association with inhibitor development, using clinical data, demographics, and genetic data from 298 participants of the INSIGHT study with nonsevere hemophilia A. They found no increased risk for inhibitor development with any FVIII concentrate.[17] Li et al used logistic regression and linear regression to explore the relationship between interval-time and low-dose immune tolerance induction in 47 severe hemophilia A children, using self-collected clinical data and demographics. They used AUC and found that shorter interval time is associated with a higher success rate.[16] Ai et al used the Cox proportional hazards model and the two machine learning methods, random survival forest and DeepSurv, to predict bleeding risk in 98 male children with severe or moderate hemophilia A. They used self-collected clinical data, demographics, pharmacokinetics/drug efficacy, and physical/functional assessments. Their random survival forest model performed best based on evaluation with C-index, Brier score, and Kaplan–Meier curve.[15]

Digital Application

Babington-Ashaye et al investigated the chatbot Saytù Hemophilie for improving education and self-management in participants with hemophilia, using psychosocial/quality of life assessments from 57 diseased participants. The app received a system usability scale (SUS) score of 81.7 showing good usability of the system.[30]

Diagnosis

Artificial Intelligence

Singh et al introduced a new preprocessing method called position-specific mutation, comparing it with one-hot encoding. They used genetic data from 6,286 participants with hemophilia A from EAHAD and evaluated their method with accuracy, recall, and precision, finding it delivered

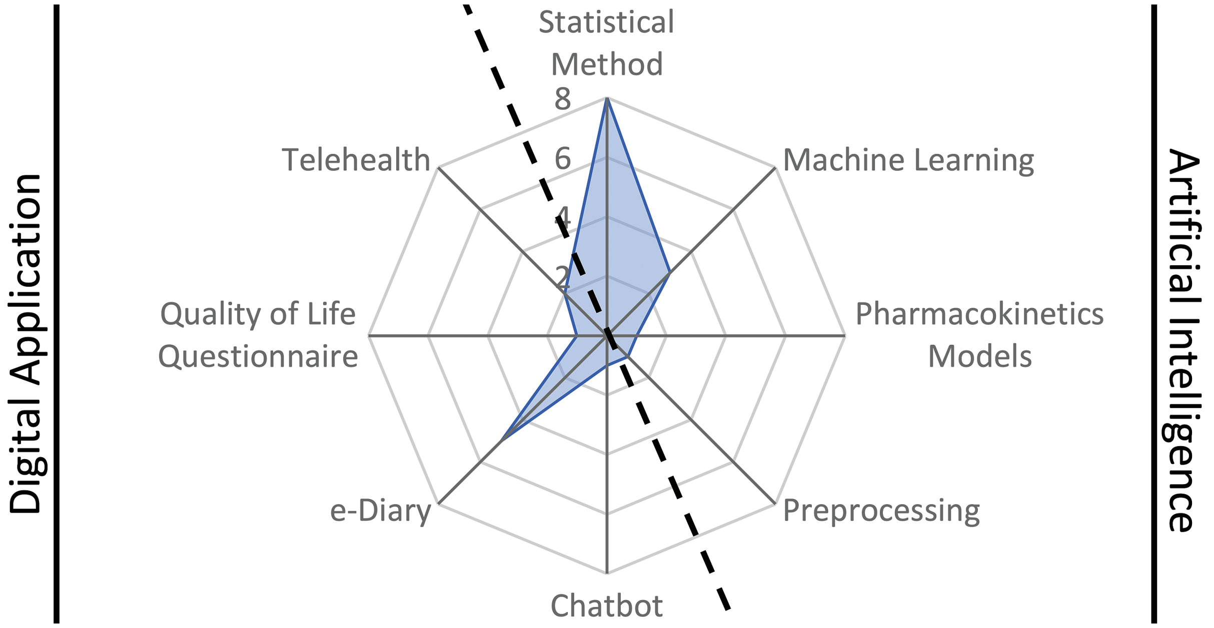

Fig. 2 Kinds of used tools and their frequencies.

Table 1 Prevention

Study	PMIDs	Study focus (prevention/ diagnosis/ treatment)	Tool purpose (short description)	Study duration	Total participants	Number of diseased participants	Number of healthy controls	Tool users/ training set size	Non-tool users/test set size	Study Type (Prospective / Retrospective)	Detailed study design	Dataset type	Existing dataset name (if applicable)	Used kind of data	Age structure	Coagulation disorder	Participation duration	Ethnicity	Gender ratio	Study location	Intervention type	Digital tool (digital application/AI)	Kind of tool used	Name of tool/ algorithm used	Smartphone optimization	User type	Research methodology	Evaluation metric (if quantitative)	Findings (short summary)
van Velzen et al[17]	32201943	Prevention	Identification of FVIII concentrate association with inhibitor development	<NA>	298 (INSIGHT cohort 2709)	75	223	298	<NA>	Retrospective	Case–control study	Existing dataset	INSIGHT study	Clinical data, demographics, genetic data	<NA>	Non-severe hemophilia A	<NA>	96% Caucasian	<NA>	Australia, Europe	None	AI	Statistical method	Logistic regression	No	Scientist	Quantitative	Odds ratios	No increased risk for inhibitor development for any FVIII concentrate
Li et al[16]	36934482	Prevention	Exploration of interval-time and low-dose immune tolerance induction relationship	September 2016–June 2022	47	47	0	<NA>	<NA>	Retrospective	Data analysis (secondary use)	Self-collected dataset		Clinical data, demographics	Mean: 7.5 mo (range: 0–62 mo)	Severe hemophilia A	<NA>	<NA>	<NA>	China	None	AI	Statistical method	Multivariate logistic regression, linear regression	No	Scientist	Quantitative	AUC	Shorter interval-time associated with higher success rate
Ai et al[15]	37931538	Prevention	Prediction of bleeding risk	June 2021–December 2022	98	98	0	80% (5-fold cross validation)	20% (5-fold cross validation)	Retrospective	Data Analysis	Self-Collected Dataset		Clinical data, demographics, pharmacokinetics/ drug efficacy, physical/ functional assessments	Median: 7.9 y	Severe and moderate hemophilia A	<NA>	Chinese (title)	100% Male	China	None	AI	Statistical method/machine learning	Cox Proportional Hazards Model, Random Survival Forests, DeepSurv	No	Scientist	Quantitative	C-Index, Brier Score, Kaplan-Meier Curve	Random survival forest model had best performance
Babington-Ashaye et al[30]	37347648	Prevention	Improvement of education and self-management	April 2022–not specified	57	57	0	57	<NA>	Prospective	Usability Study (Mixed Methods)	Self-Collected Dataset		Psychosocial/ quality of life assessments	Median: 32 y (range: 8–61 y)	Hemophilia	<NA>	<NA>	68.4% male, 31.6% female	Senegal	Training/ Education	Digital application	Chatbot	Saytù Hemophilie	Yes	Patient	Quantitative and qualitative	Mean, SD, SUS	SUS score of 81.7

Table 2 Diagnosis

Study	PMIDs	Study focus (prevention/diagnosis/treatment)	Tool purpose (short description)	Study duration	Total participants	Number of diseased participants	Number of healthy controls	Tool users/training set size	Non-tool users/test set size	Study type (prospective/retrospective)	Detailed study design	Dataset type	Existing dataset name (if applicable)	Used kind of data
Shepherd et al[18]	25244644	Diagnosis	Personalization of inhibitor risk prediction based on FVIII genotype	<NA>	1262	98	1164	<NA>	<NA>	Retrospective	Data analysis	Existing dataset	HADB (http://hadb.org.uk/)	Genetic data
Lyons et al[12]	30224115	Diagnosis	Identification of individuals with hemophilia A	1 January 2006–30 April 2015	400 with labeling, 2252 in total	<NA>	<NA>	95% (20-fold cross-validation)	5% (20-fold cross-validation), + 1852 without labeling	Retrospective	Data analysis (secondary use)	Existing dataset	US HealthCore Integrated Research Database	Administrative data
Singh et al[14]	32927010	Diagnosis	Comparison of One-Hot Encoding and Position-Specific Mutation	<NA>	6286	6286	0	<NA>	<NA>	Retrospective	Data analysis	Existing dataset	EAHAD	Genetic data
Chowdary et al[22]	34865209	Diagnosis	Prediction of annualized bleeding	<NA>	161–166	161–166	0	<NA>	<NA>	Retrospective	Data analysis	Existing dataset	Pathfinder 2 study	Clinical data, demographics, pharmacokinetics/drug efficacy, physical/functional assessments
Cruz-Montecinos et al[31]	35201643	Diagnosis	Investigation of impaired neural control of gait, pain, and joints	<NA>	37	22	15	<NA>	<NA>	Prospective	Observational analytical cross-sectional study	Self-collected dataset		Physical/Functional assessments

Age structure	Coagulation disorder	Participation duration	Ethnicity	Gender ratio	Study location	Intervention type	Digital tool (digital application/AI)	Kind of tool used	Name of tool/algorithm used	Smartphone optimization	User type	Research methodology	Evaluation metric (if quantitative)	Findings (short summary)
<NA>	Non-severe hemophilia A	<NA>	<NA>	<NA>	<NA>	None	AI	Machine learning	Artificial neural network	No	Scientist	Quantitative	<NA>	Predicts potential inhibitor risk
Mean: 34.7 y (SD: 24.6); all: mean: 30.7 (SD: 22.7)	Hemophilia A	<NA>	<NA>	81.2% Male	USA	None	AI	Statistical method	Lasso regression	None	Scientist	Quantitative	Precision (positive predictive value), ROC, recall (sensitivity, true positive rate)	High precision and high recall
<NA>	Hemophilia A	<NA>	<NA>	<NA>	<NA>	None	AI	Preprocessing	One-hot encoding vs. proposed position-specific mutation on KNN, AdaBoost, SVM, random forest	No	Scientist	Quantitative	Accuracy, Recall (Sensitivity, True Positive Rate), Precision (Positive Predictive Value)	Comparable results, reduced computational cost for position-specific mutation
Mean: 30.5 y (SD: 12.3)	Severe hemophilia A	<NA>	<NA>	<NA>	<NA>	None	AI	Statistical method	Penalized logistic regression, random forests	No	Scientist	Quantitative	AUROC	Identification of which prophylaxis variables act as predictors of clinical response
Diseased: mean: 32.3 y (SD: 11.6); healthy control: mean: 31.5 y (SD: 10.1)	Hemophilic arthropathy	1 Day	<NA>	100% Male	Chile	None	AI	Statistical method	Multiple regression	No	Scientist	Quantitative	Kappa statistic	dynamic motor control index during walking correlates with joint damage and pain

Table 3 Treatment

Study	PMIDs	Study focus (prevention/ diagnosis/ treatment)	Tool purpose (short description)	Study duration	Total participants	Number of diseased participants	Number of healthy controls	Tool users/ training set size	Non-tool users/test set size	Study type (prospective/ retrospective)	Detailed study design	Dataset type	Existing dataset name (if applicable)	Used kind of data
van Velzen et al[21]	28440011	Treatment	Assessment of association between intensive treatment and increased risk of inhibitor development	<NA>	298 (INSIGHT cohort 2709)	75	223	298	<NA>	Retrospective	Case–control study	Existing dataset	INSIGHT study	Clinical data, demographics, genetic data
Chelle et al[13]	31115857	Treatment	Pharmacokinetic modeling	Ongoing (extracted 18 February 2018)	92	92	0	90% (10-fold cross validation)	10% (10-fold cross validation)	Retrospective	Population pharmacokinetic modeling study	Existing dataset	WAPPS-Hemo	Clinical data, demographics, pharmacokinetics/ drug efficacy
Janssen et al[19]	38100092	Treatment	Validation of deep compartment model on a small dataset	<NA>	500 simulated out of 119 real patients	500 simulated out of 119 real patients	0	20, 60, 120	480, 440, 380	Retrospective	Data analysis	Existing Dataset	OPTI-CLOT trial	Clinical data, pharmacokinetics/ drug efficacy
Janssen et al[20]	38100100	Treatment	Explanation of interindividual variability for pharmacokinetics	<NA>	119	119	0	90% (10-fold cross validation)	10% (10-fold cross validation)	Retrospective	Data analysis (secondary use)	Existing dataset	OPTI-CLOT trial	Clinical data
Jacobson and Hooke[28]	26510644	Treatment	Videoconferencing support in case of acute bleeding	<NA>	12	12	0	3	<NA>	Prospective	Feasibility study	Self-collected dataset		Clinical data, psychosocial/ quality of life assessments
Hay et al[11]	28806858	Treatment	Treatment documentation	2008–2015	1807 (composition unclear)	1807 (composition unclear)	0	1192	615	Retrospective	Data analysis (secondary use)	Self-collected dataset		Clinical Data
Cuesta-Barriuso et al[23]	29493864	Treatment	Improvement of adherence to prophylactic treatment	<NA>	43	43	0	43	<NA>	Retrospective	Usage analysis	Self-collected dataset		Psychosocial/ quality of life assessments
Mondorf et al[25]	30620988	Treatment	Patient self-treatment surveillance	2012–2014	246	246	0	246	<NA>	Retrospective	Usage analysis	Self-collected dataset		Clinical data
Banchev et al[24]	30654393	Treatment	Improvement of adherence to prophylactic treatment	<NA>	100	100	0	100	<NA>	Retrospective	Usage analysis	Self-collected dataset		Administrative data, clinical data
Tiede et al[27]	33084135	Treatment	Assessment of documentation quality and adherence to prophylactic treatment	January 2019—not specified	796 (subgroup: 202)	796 (subgroup: 202)	0	796 (subgroup: 202)	<NA>	Retrospective	Usage analysis	Self-collected dataset		Administrative data, clinical data
Germini et al[29]	35234648	Treatment	Measurement of longitudinal patient burden and outcome	November 2017–July 2019	17	<NA>	<NA>	17	<NA>	Prospective	Usability study (mixed methods)	Self-collected dataset		Psychosocial/ quality of life assessments
Russell et al[26]	37729471	Treatment	Improvement of treatment plan accuracy	April 2020–July 2021	27	27	0	27	<NA>	Prospective	Cross-sectional observational study	Self-collected dataset		Demographics, physical/ functional assessments

Age structure	Coagulation disorder	Participation duration	Ethnicity	Gender ratio	Study location	Intervention type	Digital tool (digital application/ AI)	Kind of tool used	Name of tool/ algorithm used	Smartphone optimization	User type	Research methodology	Evaluation metric (if quantitative)	Findings (short summary)
<NA>	Nonsevere hemophilia A	<NA>	96% Caucasian	<NA>	Australia, Europe	None	AI	Statistical method	Logistic regression	No	Scientist	Quantitative	Odds ratios	High-dose FVIII treatment and surgery increases risk of inhibitor development
<NA>	Hemophilia A	<NA>	<NA>	<NA>	<NA>	None	AI	Pharmacokinetics models	NONMEM	No	Scientist	Quantitative	Objective function value	Two-compartment model works best
<NA>	Hemophilia A	<NA>	<NA>	<NA>	The Netherlands	None	AI	Machine learning	Deep compartment model (neural network + ordinary differential equations)	No	Scientist	Quantitative	Accuracy	Remains stable
Median: 39.8 y (range: 0.24–77.7 y)	Hemophilia A	<NA>	<NA>	<NA>	The Netherlands	None	AI	Statistical method	Random forest, XGBoost	No	Scientist	Quantitative	Feature importance, mean absolute SHAP value, mean absolute error (MAE), root mean squared error (RMSE), SD	Disclosure of subtle effects from covariate combinations difficult to detect
Mean: 10.25 y (range: 2–18 y)	Severe hemophilia	1 y	<NA>	100% Male	USA	Real-time detailed assessment	Digital application	Telehealth	Videoconferencing	No	Patient and practitioner	Quantitative and qualitative	Quantitative Questionnaire Evaluation	Helpful by patients/ families and staff
Median: 25 (IQR: 13–39), mean: 27.28 (SD: 17.56)	Hemophilia A	<NA>	<NA>	<NA>	UK	None	Digital application	e-Diary	Haemtrack	Yes	Patient	Quantitative	Median, ratio	Improvement of treatment compliance and analysis
Mean: 25.8 y (SD: 10.3)	Hemophilia A, hemophilia B	1 y	<NA>	<NA>	Spain	None	Digital application	e-Diary	Medtep Hemophilia	No	Patient	Quantitative	Mean, SD	Improvement in prophylactic treatment adherence, increased quality of life and illness perception
<NA>	Hemophilia A, hemophilia B	<NA>	<NA>	<NA>	Germany	None	Digital application	e-Diary	Smart medication	Yes	Patient and practitioner	Quantitative	Mean	Better surveillance of home treatment
Median: 41 y (range: 4–78 y)	Hemophilia A/ hemophilia B (99), severe factor VII deficiency (1)	3.5–4 y	<NA>	<NA>	Germany	None	Digital application	e-Diary	Haemoassist	Yes	Patient	Quantitative	Ratio, mean, SD	Significant advantage in data recording and tracking, improvement in compliance to prescribed treatment
Mean: 30.0 y (SD: 18.5); subgroup: mean: 24.8 y (SD: 17.3)	Hemophilia A, hemophilia B, von Willebrand disease	Average: 20 mo	<NA>	<NA>	Germany, Spain	None	Digital application	e-Diary	Haemoassist 2	Yes	Patient and practitioner	Quantitative	Ratio, median, SD	Improve adherence through reminders and accuracy of documentation by real-time reporting
Range: 23–67 y	Hemophilia	<NA>	<NA>	<NA>	Canada, Ireland, Italy, Switzerland, USA	Creation of a mobile application	Digital application	Quality of life questionnaire	myPROBE App	Yes	Patient	Quantitative and qualitative	System usability scale (SUS)	SUS score of 85, released in 81 countries and 34 languages
18–25 y: 10, 26–40 y: 20, 41–60 y: 4, 61+ y: 6	Severe hemophilia A, severe hemophilia B, severe von Willebrand disease	<NA>	<NA>	95% male, 5% female	Australia	Video conference	Digital application	Telehealth	eHAB and Queensland Health Telehealth Portal (audio- and videoconferencing)	No	Patient and Practitioner	Quantitative	Clinician confidence, SUS	Clinician confidence increased from 70.0 to 93.0% from audio- to videoconferencing

comparable results with reduced computational costs.[14] Shepherd et al employed artificial neural networks to personalize the prediction of inhibitor risk using genetic data from 1,262 participants, including 98 participants with nonsevere hemophilia A from HADB. Their evaluation methods remain unknown.[18]

Three studies utilized statistical methods. Lyons et al used administrative data from 400 labeled and 1,852 unlabeled participants from the U.S. HealthCore Integrated Research Database to identify individuals with hemophilia A. They trained a lasso regression model with 20-fold cross-validation, achieving high precision and recall results.[12] Cruz-Montecinos et al used self-collected physical/functional assessments from 37 male participants, including 22 with hemophilic arthropathy, to investigate impaired neural control of gait, pain, and joints in hemophilic arthropathy. They evaluated their approach with the kappa statistic, finding that the dynamic motor control index during walking correlates with joint damage and pain.[31] Chowdary et al used logistic regression and random forests to predict annualized bleeding in 161 to 166 participants with severe hemophilia A. They used clinical data, demographics, pharmacokinetics/drug efficacy, and physical/functional assessments from the Pathfinder 2 study, employing area under the receiver operating characteristic curve (AUROC) to identify prophylaxis variables as predictors of clinical response. Their best logistic regression model achieved an AUROC of 0.724, while their best random forest model reached an AUROC of 0.785.[22]

Treatment

Artificial Intelligence

Chelle et al used NONMEM for pharmacokinetic modeling of Fanhdi/Alphanate in 92 participants with hemophilia A. They trained the model with 10-fold cross-validation on clinical data, demographics, and pharmacokinetics/drug efficacy from the WAPPS-Hemo dataset, measuring outcomes with the objective function value. The two-compartment model worked best.[13]

Janssen et al validated a proposed deep compartment model on 500 simulated datasets based on clinical data and pharmacokinetics/drug efficacy of 119 real participants with hemophilia A from the OPTI-CLOT trial. They found that their proposed model remained stable based on accuracy.[19] In another study, Janssen et al investigated the explanation of interindividual variability for pharmacokinetics using clinical data of the 119 participants with hemophilia A. They trained random forest and XGBoost models with 10-fold cross-validation, evaluating feature importance, mean absolute SHAP value, mean absolute error (MAE), root mean squared error (RMSE), and standard deviation (SD), finding subtle effects from covariate combinations that are difficult to detect.[20] van Velzen et al used logistic regression to calculate odds ratios assessing the association between intensive treatment and increased risk of inhibitor development, using clinical data, demographics, and genetic data from 298 participants of the INSIGHT study with nonsevere hemophilia A. They found that high-dose FVIII treatment and surgery increase the risk of inhibitor development.[21]

Digital Application

Two studies investigate telehealth. Jacobson and Hooke used videoconferencing to support in case of acute bleeding using clinical data and psychosocial/quality of life assessments from 12 self-collected male participants with severe hemophilia. Three participants ultimately used the tool, and it was evaluated using a quantitative questionnaire, finding that videoconferencing is helpful for patients/families and staff members.[28] Russell et al compared audio- and videoconferencing tools in terms of treatment plan accuracy improvement, employing eHAB and Queensland Health Telehealth Portal with 27 patients with severe hemophilia A, severe hemophilia B, or severe von Willebrand disease. They collected demographics and evaluated their methods with clinician's confidence and SUS, finding that clinician's confidence increased from 70.0 to 93.0% from audio- to videoconferencing.[26]

Five studies investigated e-diaries. Hay et al used Haemtrack to document the treatment of 1,192 participants with hemophilia A, collecting clinical data and comparing it against 615 participants with hemophilia A who did not use the digital application. They used median and ratio to find improvement in treatment compliance and analysis.[11] Cuesta-Barriuso et al investigated adherence to prophylactic treatment of 43 participants with hemophilia A or B with Medtep Hemophilia. They collected psychosocial/quality-of-life assessments and evaluated them with mean and SD. They found an improvement in prophylactic treatment adherence and quality-of-life/illness perception.[23] Mondorf et al investigated smart medication for patient self-treatment surveillance. They collected clinical data of 246 participants with hemophilia A or B and found out that the digital application, on average, ensured better surveillance of home treatment.[25] Banchev et al investigated the adherence to prophylactic treatment with Haemoassist, and Tiede et al with Haemoassist 2. Both used administrative data and clinical data. Both used ratio, mean, and SD and found that digital applications increased treatment adherence.[24,27]

Germini et al employed a quality-of-life questionnaire to longitudinally assess patient burden and outcomes among 17 individuals with hemophilia. They collected psychosocial/quality of life assessments using the myPROBE app, available in 81 countries and 34 languages. It received a SUS score of 85.[29]

Discussion

In this systematic review, we comprehensively investigated the use of digital tools in the field of hereditary coagulation diseases. The search identified a total of 21 publications. Of these, 12 were focused on AI technologies, while the remaining nine explored digital applications. The integration of digital tools in healthcare for hereditary coagulation disorders represents a significant advancement. AI-driven approaches have the potential to enhance diagnostic accuracy, predict disease progression, and personalize treatment plans. Despite these advancements, the current literature reflects early-stage developments in retrospective studies.

Larger-scale studies, certification as medical devices, and broader clinical implementation remain necessary steps to fully harness the potential of these technologies in practice, aspects which were notably absent in the reviewed articles. Furthermore, the studies focusing on digital applications highlighted the development and implementation of software aimed at improving patient care. These digital applications included telehealth platforms and (mobile) health apps, all designed to facilitate better disease management and patient engagement. Five out of nine studies were prospective.[26,28–31] Among these, four studies involved some form of intervention.[26,28–30] Jacobson and Hooke employed videoconferencing to support cases of acute bleeding events.[28] Germini et al utilized a quality-of-life questionnaire to longitudinally assess patient burden which could influence treatment decisions through the study.[29] Russel et al compared audio- and videoconferencing tools, evaluating their effectiveness in improving the accuracy of treatment plans.[26] Babington-Ashaye et al explored the use of a chatbot to enhance education and self-management among participants.[30] While these interventions were primarily practitioner-driven through digital applications, direct patient interventions based on digital applications or AI-generated decisions are notably absent. For instance, AI could be utilized to detect patterns indicative of potential disorders within patient data even before a blood sample is taken, helping to determine who should undergo further investigation. Another application could be in customizing treatment recommendations, such as adjusting dosages based on specific scenarios or general coaching on lifestyle. Similar applications and tools are available, for example, in cardiology,[32,33] cancer management,[34] or pain management.[35]

In conclusion, while digital innovations show considerable promise for managing hereditary coagulation disorders, further research and development are imperative to bridge the gap between feasibility studies and widespread clinical application. This journey entails rigorous validation, regulatory certification, and robust clinical trials to substantiate their effectiveness and ensure their safe integration into healthcare practice.

The findings of this review underscore the growing importance of digital innovations in managing hereditary coagulation disorders. Further research and development in this area are essential to fully realize these technologies' potential.

Study Biases

Most studies were conducted in Western countries[11,12,17,19–21,23–29] or did not specify their location.[13,14,18,22] Only four studies were conducted outside of Western countries: two in China,[15,16] one in Chile,[31] and one in Senegal.[30]

Gender ratio information was absent in 15 studies,[11,13,14,16–25,27,29] while some were exclusively conducted on male participants.[15,28,31] Only three studies included data from both genders, but male predominated.[12,26,30] Participant ethnicities were generally unclear, with only two studies specifying that 96% of participants were Caucasians[17,21] and one specifying that the participants were Chinese.[15]

A majority of studies (12) focused exclusively on hemophilia A[11–22] or general hemophilia.[28–30] Five studies also included hemophilia B alongside hemophilia A,[23–27] and two studies included von Willebrand disease in addition to hemophilia A and B.[26,27] Only one study focused on hemophilic arthropathy,[31] and none focused exclusively on hemophilia B or von Willebrand disease.

Of the 12 AI studies, only four included healthy controls.[17,18,21,31] One study did not specify its control group,[12] and seven studies did not include healthy controls.[13–16,19,20,22]

In summary, while the geographical distribution of the studies shows a heavy bias toward Western countries, it is important to note that hereditary coagulation disorders occur globally,[36] and therefore this bias may limit the generalizability of the findings. Research should ideally reflect this worldwide prevalence to ensure the generalizability of findings. The gender distribution, predominantly male, is understandable given that these disorders, particularly hemophilia, predominantly affect males. The focus on hemophilia A is justified as it is the most common type of hemophilia; yet, the lack of studies on other hereditary coagulation disorders, such as von Willebrand disease and hemophilia B, indicates a gap in the research. The absence of healthy controls in many studies also highlights a limitation in study design, potentially affecting the robustness of the findings.

Several of the included studies were authored by individuals with conflicts of interest (e.g., received funding from programs associated with pharmacological companies), potentially influencing the impartiality of their reported results.[11–13,17,18,21–25,27,29,30] Such biases may compromise the validity of the findings and should be considered when interpreting the conclusions.

Limitations

Since the focus was on medical terminology, the search was limited to PubMed, which may have excluded relevant studies indexed in other medical and multidisciplinary databases such as Embase, Cochrane Library, and Web of Science. The authors found this limitation acceptable, as the focus of the review is the impact of digital tools on the healthcare system and not specific digital methodology implementations that are only validated on clinical for convenience purposes.

Only English-language articles were considered in the review, which is a limitation as relevant studies published in another language are not included. This filter criterion may lead to a language bias and limits the generalizability of the results.

Conclusion

This systematic review provides a comprehensive overview of current research on the application of digital technologies in managing hereditary coagulation disorders. The integration of AI and digital applications shows promising advancements in the prevention, diagnosis, and treatment of these complex conditions. AI technologies, including machine learning and statistical methods, demonstrate potential for enhancing diagnostic accuracy, predicting disease progression, and personalizing treatment plans based on individual patient data.

Digital applications, such as mobile health apps and telemedicine platforms, offer innovative solutions to improve patient care, enhance adherence to treatment regimens, and facilitate remote consultations. These tools are particularly beneficial for patients in remote or underserved areas. These tools not only aim to streamline healthcare delivery but also empower patients by providing them with tools to manage their conditions more effectively.

Despite these advancements, several challenges and limitations were identified. The geographical bias toward Western countries and the predominance of male participants in many studies may limit the generalizability of findings globally. Additionally, the lack of large-scale prospective studies and standardized clinical trials, especially with digital interventions, hinders the broader implementation and validation of these digital innovations in clinical practice.

Further research is crucial to address these gaps and validate the effectiveness, safety, and scalability of digital technologies in managing hereditary coagulation disorders. Future studies should aim to include diverse patient populations, conduct prospective trials, and adhere to rigorous methodological standards to facilitate the integration of these technologies into routine clinical care. By overcoming these challenges, digital innovations hold substantial promise in improving outcomes and quality of life for patients with hereditary coagulation disorders worldwide.

Authors' Contributions

F.K., M.K., and S.M.J. conceived and designed the analysis. M.K. extracted titles and abstracts from PubMed and applied the automatic filtering by date range and language. All authors equally participated in the double-checked screening of titles and abstracts for inclusion. F.K., M.K., and L.N. handled conflicts in titles and abstract inclusion. During the full-text screening, F.K. reviewed all the articles, while the other authors screened the articles by equally sharing among them, ensuring double-checking. Information extraction from the full articles was performed, with F.K. handling all articles and the remaining workload was equally shared among the others, and also double-checked. F.K. wrote the manuscript, which was critically revised by all authors. They provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, we used generative AI to proofread the text and eliminate typos and grammatical flaws. After that, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

Funding

This research did not receive any specific grant from public, commercial, or nonprofit funding agencies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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