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Big Data–Driven Machine Learning Frameworks for Clinical Risk Prediction

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ABSTRACT
Healthcare is a path-breaking field for big data. By combining electronic medical record data with omics data (genomics, proteomics, metabolomics, etc.), lifestyle information (e.g., smoking, drinking, diet, and exercise), social determinants of health, and relevant data from wearable devices, a diverse array of clinical and biological predictive models can be constructed. In particular, the application of machine-learning (ML) methods for clinical risk-prediction modeling has gained impressive momentum in recent years, amassing a wealth of reference literature. Unlike traditional statistical approaches commonly utilized in clinical applications, ML techniques have the potential to simultaneously leverage high-dimensional, heterogeneous data.
This contribution reviews multiple important aspects of risk prediction using big data and ML methods, including data-sources, framework, performance metrics, and regulation. Relevant clinical applications span almost every area, including cardiovascular medicine, oncology, infectious diseases, nephrology, rheumatology, and psychiatry. Although numerous ML-based risk-scoring systems with impressive performance are found in the literature, external validation and transportability remain critical challenges that merit further exploration.

Keywords : Combining PC-1; PC-2 with ML Ridge regression; SVM Linear; lasso; AUC-ROC curve; area under the precision-recall; maximal accuracy Ya.Yu. et al.; the goodness of fit was evaluated and an internal; external validation of the risk score Risk factors; sensitive; specific; especially; AUC-ROC 3829 clinical/biobanked; 110706 clinically well-characterized; 7400 clinical; 165237 individuals.

1. INTRODUCTION

Big data, involving high-velocity, high-volume, and high-variety data feeds, presents multiple challenges. However, these features confer the ability to comprehend dynamic processes at various resolutions, enabling the extraction of critical and useful patterns. Utilizing these properties requires a multi-disciplinary effort across several engineering disciplines and presents challenges in automation. New data sources and consumer-facing applications, such as smart homes, connected vehicles, and mobile communications, are constantly emerging and can influence industry practice and business models. The health domain, where a large amount of data is generated every day, and massive amounts of data from heterogeneous sources are available, provides one of the best platforms for validating big data theories and techniques. Healthcare covers smart living services, personalised medical services, and ubiquitous health monitoring.
In recent years, the importance of clinical risk prediction for individual patients has been recognised. Comprehensive data from different sources can support trustworthy machine learning frameworks and yield efficient predictive models for individual patients. High-dimensional risk-scoring systems do not provide sufficient coverage and stability for most variables in high-dimensional space; combining supervised learning methods and risk scoring can alleviate these two problems. The introduction of big-data-driven machine learning frameworks is a promising direction for building personalised prediction models.

1.1. Background and Significance

The clinical and public health importance of accurate risk prediction is widely acknowledged; intentionally or unintentionally, clinicians constantly assess patients' risk of symptoms or disease. When clinicians' intuitive assessments are not quantifiable, predictive models developed with large datasets of patients can help clinicians estimate the joint effects of multiple patient characteristics. Traditional statistical risk models, such as logistic regression, can overcome these limitations for a target population by providing continuous risk score estimates. However, the increasing availability of self-reported, continuous, and high-volume healthcare data from different sources has made the development of superficially more advanced machine-decision support models particularly attractive. Machine learning applies to a broader array of predictive problems than traditional

statistical models and can discover common structures in the data without making strong assumptions, leading to increased prediction accuracy.

In addition, there is a growing consensus that traditional statistical analysis methods should be clearly differentiated from modern machine learning methods. Although the term "machine learning" remains poorly defined, it is currently commonly used in situations in which prediction accuracy is the primary goal of model training or selection. In medicine, a reasonable interpretation of this viewpoint is that, when prediction is the primary goal, prediction accuracy should be measured with explicitly held-out test data not used in model training or selection. In consequence, risk scoring based on supervised machine learning approaches enables building continuous risk-scoring functions for predicting future events of interest. A role in linking Big Data and clinical risk prediction using supervised machine learning techniques is developed by presenting frameworks for Big Data ingestion, preparation, and risk-score generation, while discussing the connections between Big Data and the clinical domains of cardiovascular disease and cancer.

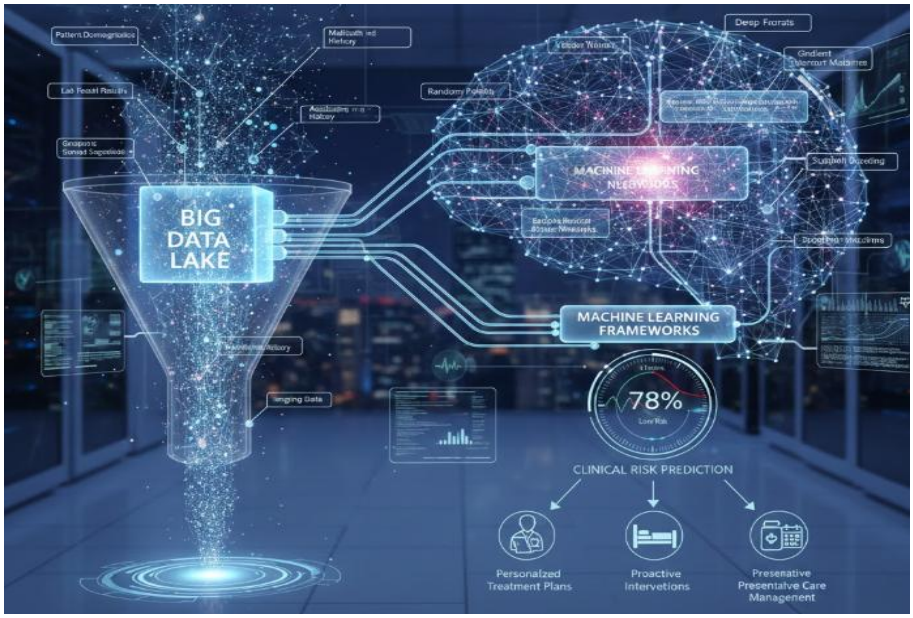


Fig 1: Big Data–Driven Machine Learning Frameworks

1.2. Research design

A comprehensive review of clinical risk prediction methodologies, relying on supervised machine learning, is presented. The focus is on a dedicated type-III framework that utilizes risk scores estimators, which can be valuable for patients, physicians, healthcare organizations, and insurers. Such models predict risks of occurrence for primary outcomes as well as risks of developing secondary outcomes, providing a complete clinical risk profile. Typical applications include predicting concurrent cardiovascular disease (CVD) and Type 2 diabetes, the combined risk of coronary heart disease and breast cancer, and the simultaneous risk of clinical CVD and cancer.

Big data infrastructures for clinical prediction powered by supervised machine learning are reviewed, synthesizing existing work and guiding future endeavors. First, state-of-the-art experimental pipelines that collect, harmonize, and curate data from a variety of health information systems are examined, creating integrated databases containing large volumes of high-dimensional patient information. Next, the emphasis shifts to data representation, exploring techniques focused on feature engineering and automatic feature learning from raw data. Finally, the discussion covers performance evaluation of the resulting models, good clinical practice of machine learning, separation between model development, evaluation, and application, and considerations regarding the transportability of predictive models.

2. Foundations of Big Data in Healthcare

Volume, variety, and velocity describe the three dimensions of Big Data. Health information must also satisfy requirements for public and private governance. Regulatory frameworks guarantee the adequate processing of sensitive data, thus enabling clinical research. Technological evolution has allowed the integration of multiple data sources and types in large databases. These sources include the electronic health record, which contains information on patient clinical history, and wearable devices, which collect data on physical activities, vital signs, and the external environment. Integration of such data enables the assessment and prediction of health and disease through classical statistical techniques and modern machine-learning (ML) approaches.

The integration of these two sources leads to prediction models that combine clinical and behavioral characteristics for cardiovascular disease (CVD) risk stratification. Such models predict the probability of CVD events on the basis of clinical features. Previous studies estimated the prognostic value of combining supervised clinical risk scores with interim information on lifestyle changes derived from unconstrained 7-day pedometer recordings. The models explored the effect of counseling-based interventions on CVD risk at 1 year. The results demonstrated the potential of additionally including bidirectional–individual-centric information in the prediction of disease. Furthermore, they proposed an innovative ML architecture for the estimation of risk scales in the middle-term temporal range.

Equation 1: Logistic regression (classic risk score baseline)
Step 1: Model probability with the sigmoid
Let the linear predictor be

$$z_i = \beta_0 + \beta^\top X_i$$

Map it to a probability:

$$p_i = P(Y_i = 1 \mid X_i) = \sigma(z_i) = \frac{1}{1 + e^{-z_i}}$$

Step 2: Bernoulli likelihood
Because $Y_i \in \{0,1\}$,

$$P(Y_i \mid X_i) = p_i^{Y_i}(1 - p_i)^{1-Y_i}$$

For $n$independent patients:

$$\mathscr{L}(\beta) = \prod_{i=1}^{n} p_i^{Y_i}\,(1 - p_i)^{1-Y_i}$$

Step 3: Log-likelihood (easier to optimize)

$$\ell(\beta) = \log \mathscr{L}(\beta) = \sum_{i=1}^{n} [Y_i \log p_i + (1 - Y_i)\log(1 - p_i)]$$

Step 4: Negative log-likelihood = cross-entropy loss
Minimizing $-\ell(\beta)$is equivalent to minimizing:

$$\mathcal{J}(\beta) = -\sum_{i=1}^{n} [Y_i \log p_i + (1 - Y_i)\log(1 - p_i)]$$

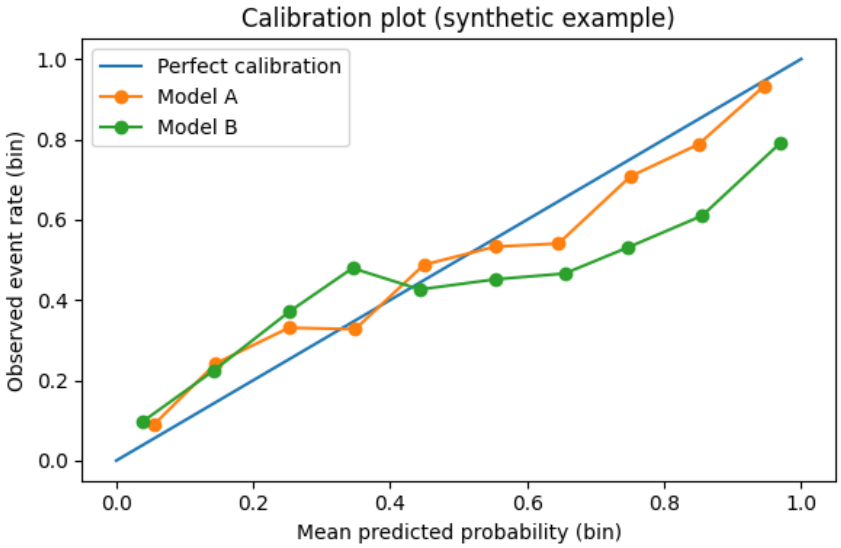
2.1. Data Sources and Data Types
To realize the vision of empowering healthcare delivery through data and evidence, it is crucial to derive actionable insights, such as clinical risk models, from the variety of structured and unstructured data generated from multiple data sources at all levels of healthcare delivery. Since all digital services, electronic health records, and sensors generate an unprecedented quantity of user-centered data on patients, caregivers, and clinicians at different levels of healthcare delivery, the growing volume of these data offers an opportunity to develop reliable, robust, and trustworthy Big Data–driven models for clinical risk prediction. A plethora of new healthcare data sources exist, but three major data categories—those containing patient-centered, caregiver-centered, and clinician-centered data—all hold the potential to derive predictions and insights about clinical risk. The patient-centered data are related to disease, treatment, and post-treatment outcomes. Caregivers are currently involved in helping patients manage chronic diseases more effectively, while clinician-centered data are mainly used for training, skill assessment, and surgical risk assessment.
Apart from traditional healthcare data sources consisting of structured data from patients and health records, new unstructured and semi-structured data sources are being generated continuously. Unstructured and semi-structured data can be mined for information to help make better clinical decisions. These include social media data (tweets, posts, articles, and blogs) that share patient experiences, reviews of hospitals, doctor ratings, news from health organizations, etc.; data from status updates; patient forums and communities; and patient and family blogs that discuss and report on the experience of a specific disease such as cancer, diabetes, or a specific mode of treatment such as dialysis. These unconventional data sources can be harnessed for modeling the correlation between sentiment and health (Saha & Shankar, 2020), predicting the volume of flu infection (Yang & Wu, 2016), predicting the severity of skin diseases (Thiyagarajan &Veloo, 2016), etc. Thus, new healthcare data sources complement existing clinical data for different applications across various domains.

2.2. Data Quality, Governance, and Privacy

Healthcare data are inherently complex because they may originate from multiple stakeholders and entities within a healthcare system. To ensure that data are conducive to proper analysis, they must be of high quality. Poor data quality can arise from incomplete, missing, or inconsistent data. An example of this is the record of a pregnant single woman who may have subsequently become divorced during the observation window and then have secondary diabetes. Without supporting multiparous cases, data with missing values can create difficulty in learning machine learning models, especially decision tree models that can handle missing values directly. Model performance in such cases can also be poor. Therefore, the missing value imputation process should be carefully designed and applied such that the characteristics of the original data can be preserved.

Proper data governance mechanisms should be put in place to monitor the accessibility of data in a healthcare system in accordance with legal and regulatory requirements. For Big Data analysis in healthcare, the establishment of a healthcare data commons can be considered. Such a data commons can then serve as a research and collaboration platform for transnational Big-Data-driven research. Because health data also reflect sensitive information about each individual's physical condition, errors in the prediction model may lead to the disclosure of sensitive ground truth labels. A robust defence mechanism against data leakage should therefore be carefully designed and deployed.

Proper data governance mechanisms are essential to ensure that data accessibility within healthcare systems is continuously monitored and aligned with applicable legal, ethical, and regulatory requirements. As Big Data analytics becomes increasingly central to healthcare innovation, the establishment of a healthcare data commons offers a promising approach to facilitate secure, standardized, and collaborative data sharing across institutions and national boundaries. Such a commons can function as a trusted research infrastructure that promotes transnational Big-Data-driven studies while enforcing clear policies on data stewardship, accountability, and usage rights. However, given that health data inherently contain highly sensitive information about individuals' physical and mental conditions, even indirect disclosures—such as those arising from model inference errors or adversarial attacks—can expose confidential ground truth labels. Consequently, robust defense mechanisms against data leakage must be carefully designed and integrated throughout the data lifecycle, including strong access controls, privacy-preserving analytics, encryption, auditing, and continuous risk assessment. Together, these measures help balance the dual imperatives of enabling data-driven discovery and safeguarding patient privacy.



3. Machine Learning Methods for Clinical Risk Prediction

Supervised learning methods, using a variety of structured data, such as demographic information along with lab results and vital parameters measured in routine hospital visits, are appropriate for just-in-time clinical risk prediction. Special considerations exist for applications using health-care data, where the model focus is measuring the risk of future adverse clinical events, such as 10-year cardiovascular risk-estimation models or cancer prediction models that aim to determine the predicted higher-risk population incidence within a timespan of 1–3 years. Risk scoring is the natural model output in either case, and ML methods provide a principled way to learn from recent data and adapt to changing patterns in the underlying population and environment.

While established clinical risk-scoring systems typically depend on simple logistic regression fitted on curated data sets reflecting expert opinions, Machine Learning (ML) models can use a larger set of candidate predictors, employ non-linear interactions between predictors, and use non-parametric assumptions. These differences can

lead to improved predictive accuracy, and research has shown that more complex methods can help identify latent subgroups. Nevertheless, the scoring ability is a special case of supervised classification in ML, and techniques designed for predicting binary outcomes remain applicable even in the presence of an underlying severity score. Classes in supervised ML, including decision trees, support vector machines, random forests, gradient boosting, or neural networks, are applicable in practice.

Traditional clinical risk-scoring systems are commonly built using logistic regression models applied to carefully curated datasets that reflect established clinical knowledge and expert judgment. While these approaches offer interpretability and transparency, they are often limited to a relatively small set of predefined predictors and assume linear relationships between variables. In contrast, Machine Learning (ML) models can incorporate a much broader range of candidate predictors, capture complex non-linear interactions, and operate under fewer parametric assumptions. These capabilities frequently translate into improved predictive performance and enable the discovery of latent patient subgroups that may not be apparent through conventional modeling techniques. Importantly, clinical risk scoring can be viewed as a specific instance of supervised classification, meaning that standard ML methods designed for binary outcome prediction remain applicable even when an underlying severity score exists. Consequently, a wide range of supervised learning algorithms—including decision trees, support vector machines, random forests, gradient boosting methods, and neural networks—can be effectively implemented in clinical practice to enhance predictive accuracy and support evidence-based decision-making.

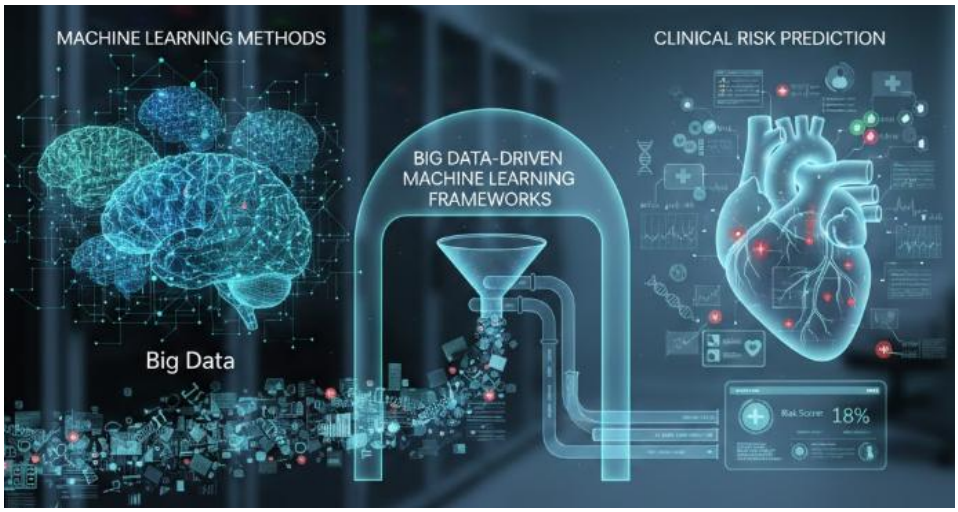


Fig 2: Machine Learning Methods for Clinical Risk Prediction

3.1. Traditional Statistical Approaches versus Modern ML

Many applications of predictive analytics for healthcare and health system data rely primarily on traditional regression-based statistical methods, including linear regression, logistic regression, Poisson regression, and numerous extensions of these general themes. Generally, the adoption of more modern machine-learning approaches has been limited. However, much of the potential improvement gain from large-scale clinical data for easing prediction posited in the literature hinges upon operating these data through state-of-the-art predictive machinery. For many clinical prediction tasks, the features known to be clinically important are available in the record and can be reliably represented; the payoff from traditional elegance is often outweighed by avoiding predictively irrelevant assumptions. Therefore, machine-learning methods are particularly well suited to these tasks. Moreover, for health systems without well-characterized prior risk models, even the direct data from the clinical record itself can allow the construction of new, state-of-the-art predictive strategies by employing the full set of features present in the record-systems infrastructure.

The predictive faculties of contemporary supervised learning remain tightly connected to the traditional risk-scoring models, but the developments of big-data strategies draw upon machine-learning tools requiring less algorithmic structure. The elements of risk-scoring models that relate to feature selection, exclusion, and transformation can be immensely valuable guides during the model-building process. However, once the traditionally important features are either selected or represented, modern predictive machinery can be applied directly to the larger data without imposing the higher-level assumption demands of logistic regression. The traditional assumption of independence among the risk factors in predicting extreme outcomes need not be held, nor is it necessary to balance the errors across the outcome classes. The extension of machine-learning developments into the future allows for the effects of ignorance of external causation to be learned directly from the relationship among the record features in the full data set.

3.2. Supervised Learning and Risk Scoring

Machine learning has a much broader scope than traditional statistical approaches, including both supervised and unsupervised learning methods. Supervised learning involves several tasks, including classification and regression, which aim to predict a target variable Y given predictor variables X . For clinical risk scoring, the most relevant methods can be classified as regression tasks, where the outcome variable Y is a continuous score indicating the probability of entering a risk state. During the development of these models, an event indicator is often generated to express whether the patient has entered the risk state that needs to be predicted (Y = 1) or not (Y = 0), considering a specific time horizon.

This event indicator is then used in supervised machine learning methods to learn a function from X to the event indicator, usually expressed as f(X) = Y. Various performance evaluations can be used to assess the quality of this learned function, which may also be integrated into the risk score. When the performance is satisfactory, the risk score is applied to other upcoming cohorts not used in building the model to classify them as entering or not entering risk states over a future time period. Consider a group of (external) validation cohorts that have not been used in building the model; the output from the index model is usually termed an external validation. Alternatively, the prediction task can be termed transportability, where other cohorts are of interest for external testing.

Equation 2: Ridge and Lasso (regularized logistic regression)

Ridge (L2) penalty

Add $\lambda \parallel \beta \parallel_2^2$to reduce overfitting:

$$\mathcal{J}_{\text{ridge}}(\beta) = -\sum_{i=1}^{n}[Y_i \log p_i + (1 - Y_i)\log(1 - p_i)] + \lambda \sum_{j=1}^{p} \beta_j^2$$

Lasso (L1) penalty

Promotes sparsity (feature selection):

$$\mathcal{J}_{\text{lasso}}(\beta) = -\sum_{i=1}^{n}[Y_i \log p_i + (1 - Y_i)\log(1 - p_i)] + \lambda \sum_{j=1}^{p} | \beta_j |$$

4. Frameworks for Big Data–Driven Clinical Prediction

Frameworks for Big Data–Driven Clinical Prediction

Designing, developing, and deploying accurate clinical risk-prediction models from heterogeneous, high-dimensional, and fast data sources often requires the use of modern Big Data technologies and tools. The framework presented comprises five critical components that together enable the building of ML-based clinical risk models. These elements track the flow of data from ingestion to modeling and can be logically decoupled into separate modules, each using different technologies, tools, and expertise.

The first component deals with data ingestion, integration, and storage: collecting data from both static and streaming data sources; cleaning, integrating, and fusing the data; and securely storing integrated patient data for later access by other pipeline modules. The second component focuses on feature engineering and representation learning: automatically generating high-quality predictive features based on raw patient data. The third component specializes in training ML models, which may involve additional tasks such as hyperparameter tuning, model selection, and optimizing feature subsets for model training.

4.1. Data Ingestion, Integration, and Storage

The architecture of a typical Big Data–driven ML framework for clinical risk prediction follows a modular and layered design. At the bottom layer, the data ingestion, integration, and storage module receives digital healthcare datasets from multiple heterogeneous sources and in various formats. Broadly, the data ingestion module often executes three main operations: (i) collection, (ii) integration, and (iii) storage.

First, data are typically collected from unique, independent data sources (e.g., healthcare provider systems and wearable devices) that may generate one or multiple data types (e.g., EHRs, laboratory tests, genomic sequencing, and imaging). These data sources often operate independently and provide data for only a small subset of patients and at discrete time points. Since patients frequently consult multiple healthcare providers, the systems of these independent providers need to interoperate for obtaining the patients' complete data records. To that end, the data ingestion module usually employs technologies such as Fast Healthcare Interoperability Resources (FHIR) and HL7 that ensure interoperability among disparate sources of healthcare data and the sharing of patients' data among different organizations and systems to obtain a holistic view of their healthcare risk.

Equation 3: Linear SVM (for "SVM Linear")
Step 1: Hard-margin idea (separable)
Find a hyperplane $w^\top x + b = 0$maximizing margin:

$$\min_{w,b} \frac{1}{2} \| w \|^2 \text{ s.t.} y_i(w^\top x_i + b) \geq 1$$

where $y_i \in \{-1, +1\}$.
Step 2: Soft-margin (real clinical data not perfectly separable)
Introduce slack $\xi_i \geq 0$:

$$\min_{w,b,\xi} \frac{1}{2} \| w \|^2 + C \sum_{i=1}^{n} \xi_i$$

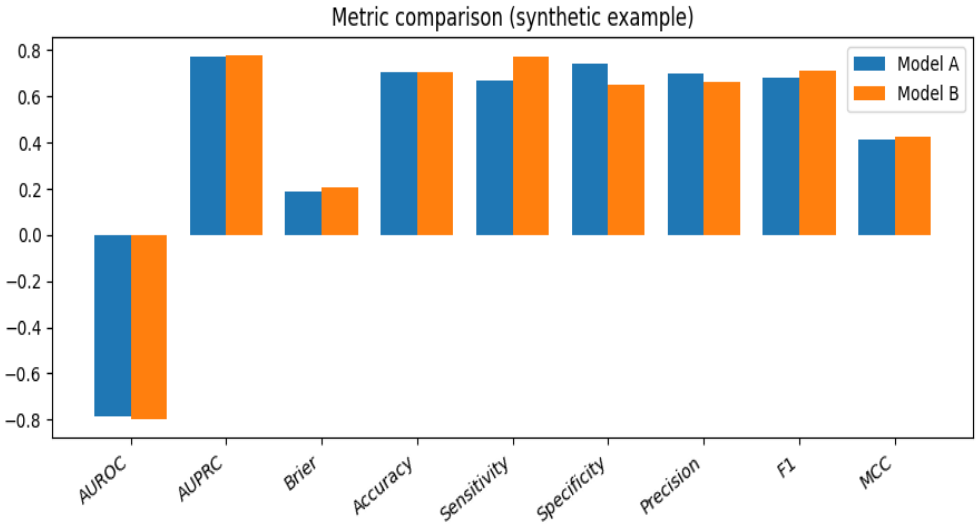
subject to

$$y_i(w^\top x_i + b) \geq 1 - \xi_i, \xi_i \geq 0$$

Step 3: Hinge-loss form (same objective, unconstrained)
This is equivalent to:

$$\min_{w,b} \frac{1}{2} \| w \|^2 + C \sum_{i=1}^{n} \max(0, 1 - y_i(w^\top x_i + b))$$

4.2. Feature Engineering and Representation Learning
Feature engineering remains a critical step in building ML-based prediction models despite the hype surrounding the capabilities of deep neural networks. Traditional machine learning algorithms such as SVM and XGBoost typically require expert-built features for optimal performance. For decision tree models particularly, carefully constructed features can be instrumental in avoiding the risk of overfitting. Domain expertise is invaluable for generating such features that can maximize predictive performance, produce easily interpretable models, and accelerate the search process in hyperparameter tuning. Feature studio platforms that combine high-quality evidence with the experience of data scientists and clinicians can facilitate and speed up the construction of relevant features based on lab tests and imaging studies, among others.
Deep learning, however, has triggered a radical shift in how data representation is learned and if feature engineering is even required. The success of deep learning methods, especially for unstructured data ranging from text to images to video, has enabled model performance to increasingly depend on the volume of data as opposed to the quality of features used. With sufficient amounts of curated training data, DNNs can learn low-, mid-, and high-level features automatically and implicitly while generalizing well on unseen data by virtue of regularization techniques that prevent overfitting. Moreover, DNNs in the form of CNNs have superior capabilities for non-Euclidean structured data such as those generated in graph-based settings as well as for images. When pretrained on large annotated datasets and subsequently fine-tuned on task-specific datasets, DNN architectures can serve as general-purpose function-approximators. In the context of clinical risk prediction from tabular data, representation learning through fixed, learned, or transferrable embeddings can also assist in shortening the search for optimal features with reduced data.



5. Evaluation and Regulatory Considerations

Performance Metrics for Clinical Risk Models. Apart from accuracy, likelihood, precision, and recall, ML methods focus on metrics such as sensitivity, specificity, area under the receiver operating characteristic curve (AUROC), area under the precision-recall curve (AUPRC), Brier score, and net reclassification improvement index (NRI). Sensitivity indicates the probability of correctly predicting a beneficial clinical outcome, whereas specificity measures the probability of correctly predicting an adverse clinical event. The AUROC provides a means of assessing the predictive performance of models that output probabilities rather than binary classifications. The Brier score is particularly useful for assessment of probabilistic predictions of binary outcomes; it measures the mean squared difference between predicted probabilities and the eventual outcomes. The NRI enables researchers to quantify the extent to which a new risk instrument provides improved clinical predictions compared to an older risk score.

External Validation and Transportability. Compared with classical statistical models, ML algorithms are often perceived to have greater flexibility in predicting outcomes across diverse patient cohorts. Characteristic heterogeneity in the patient population—e.g., age, ethnic background, sex, comorbidities, socioeconomic status—has been shown in clinical practice to affect the likelihood of patient responses to specific treatments. It is therefore clinical best practice to first evaluate model performance in the primary cohort before then validating predictions in external independent cohorts of patients. External validation, transferability, and transportability across cohorts from different geographies, health-care settings, and populations are critical areas of focus for more advanced predictive ML algorithms. Transportability is the degree to which a risk prediction function developed in one cohort can be applied in other cohorts without reestimation of the coefficients. Broadly speaking, differences in the distributions of significant risk model predictors between the model derivation cohort and the population under consideration should be minimal.

5.1. Performance Metrics for Clinical Risk Models

Risk models are evaluated with a range of performance metrics that reflect specific clinical and user requirements. Through these metrics, model developers, regulatory agencies, and end users can assess a model's performance and see whether it aligns with its intended purpose or use. Standard metrics in predictive analytics, including area under the receiver operating characteristic curve (AUC) and area under the precision-recall curve (AUPRC), summarize the predictive skill of the model under both class-imbalance and class-balance settings. AUC is a misleading metric when the positive class is very rare, whereas AUPRC is not. Thus, AUPRC is preferred, though prediction-oriented metrics such as accuracy, F1 score, Matthew's correlation coefficient, and Brier score, which assess predictive skill on the designated operating point, are often favored in clinical applications.

Bennett and Dorr provide a helpful overview of the most relevant evaluation metrics for risk models and their relative merits. These can be categorized into model fit and discrimination, calibration, or clinical utility. Fit metrics such as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) indicate how well the model approximates the training data and take into account both goodness of fit and model complexity. Discrimination measures such as get C-statistic, AUC, and gloss provide a single number that conveys how well the model distinguishes between subjects who experience the event and those who do not. Calibration measures assess the degree of concordance between predicted probabilities and observed probabilities, whereas clinical utility metrics gauging whether the model can improve clinical outcomes compared to existing alternatives.

Fig 3: Performance Metrics for Clinical Risk Models

5.2. External Validation and Transportability

As highlighted, assessing a clinical risk model's predictive performance (typically, AUC or ROC) on an independent external dataset is critical to bolster evidentiary support of its utility. The goal of recognizing the evaluation of the model on an independent external dataset with a sample size large enough to offer a meaningful test is noted. Beyond size, adequate definitional concordance of the external validation set with the derivation dataset is also essential. Additionally, the external validation cohort must remain independent from the derivation cohort with respect to individual patient membership. Transportability quantifies the performance of a risk model on population subgroups not included in the derivation dataset. For instance, a cardiovascular risk model may exhibit significant predictive performance within, say, South Asian populations or older individuals — populations not included in the original model's derivation but reported on in a smaller-scale independent study.

In domains such as cardiovascular risk prediction, routine examination of transportability has prompted numerous models to appear explicitly oriented for South Asian populations, given low clinical adoption of Western risk factors in such high-risk cohorts. When a risk score's transport ability fails validation, variance in the predictive ability of its constituent risk factors has often been implicated, justifying alternative visual approaches (such as cover plots) to illuminate precise factors driving the score's predictive power. Relying on a model's predicted probabilities underscores uncertainty and may exacerbate poor calibration, thereby muddying the signal of an external validation or transportability assessment. Difficulty in evaluating classifier-based models across stratifications of sample size, follow-up duration, and data set characteristics remains a pervasive limitation, coupled with scant dedicated scholarship on the transportability of nonstatistical machine-learning models.

Equation 4: PCA (PC1, PC2) used before ML

Step 1: Covariance matrix

$$S = \frac{1}{n-1} X^{\top} X$$

Step 2: Eigen-decomposition

$$S v_k = \lambda_k v_k$$

where v_k are principal directions, ordered $\lambda_1 \geq \lambda_2 \geq \cdots$.

Step 3: Principal component scores

PC1 scores:

$$\text{PC1} = X v_1$$

PC2 scores:

$$\text{PC2} = X v_2$$

6. Applications in Clinical Domains

Research in the domain of clinical prediction is naturally inclined toward cardiovascular disease risk typing, with efforts often focusing on either improved prediction using traditional risk factors or risk grouping based on blood biomarker testing. A meta-analysis of existing scores for coronary heart disease prediction using established clinical risk factors found that 47 % of models did not undergo external validation. More recent studies on statistical outcomes of such scores demonstrate a similar tendency toward internal validation or, in the case of machine learning, the absence of validation altogether. Consequently, the rules emerging from classical clinical risk score applications have become rather automated, similar to the plethora of new models for 10-year Framingham risk score equivalents, with the addition of novel predictors such as family history or hsCRP level. To that extent, the digital tool kit available to physicians is converging toward applicability, succinctness, and universal acceptance.

The oncology domain has seen mature and systematic application of both radiomic (i.e., ML across pre-existing image features) and pathomic (ML across pre-existing histopathological features) layer techniques, particularly in predicting recurrence risk after treatment with a curative aim and in the imaging of lung and breast cancer. Formal attempts to integrate multi-modal data in such models remain limited even in renowned datasets such as The Cancer Genome Atlas, primarily owing to the fact that most data types do not possess the spatial continuity or sparsity of image data; yet if properly implemented, the concept of data fusion holds promise for cancer care. Despite being the worst disease for prediction in clinical decision support systems, infectious disease prediction is also the domain where the greatest emphasis on precision risk typing exists, largely because the type of data available (e.g., travel flows) easily accommodates predictive mapping.

6.1. Cardiovascular Risk Prediction

Human vascular disease accounts for approximately a third of global mortality. Coronary heart disease, strokes, peripheral vascular disease, and aortic aneurysms often share common pathophysiological mechanisms and are discussed together under the heading of cardiovascular disease (CVD). Simple CVD risk models based on friality points such as age, blood pressure, smoking status, diabetes, and cholesterol levels, combined with a limited set of additional risk factors, such as family history and race, can predict either fatal or non-fatal CVD events reasonably well over 10 years. However, a more precise determination of absolute risk in patients who have not had a CVD event before is clinically valuable and may improve the impact of risk-reducing therapy.

In the Framingham Heart Study, ML methods were used to model the probability of developing coronary heart disease in a population of participants without diagnosis at baseline. The same ML models were trained for two time horizons (2 and 4 years) to explore the trade-off between predictive performance and model transparency. The five methods were used in combination (predicting with each method separately and selecting the model with lowest validation score provided) and in ensembles of two, three, or four models. The C4.5 classification tree generated the best combination of predictive discrimination and interpretability, resulting in a predictor based on a fewer number of risk factors than the traditional Framingham Heart Study point calculator.

Machine Learning–based Cardiovascular Disease Patient Open Data coupled with ML algorithms demonstrated more accurate predictive models than other linear algorithms in the identification of high-risk patients with diseases complicated by CVD. Survival analysis identified three significant factors affecting the survival of patients with coronary heart disease and associated chronic depressive symptoms: history of previous myocardial infarction, cardiac surgery, and ischemic stroke.

Equation 5: Evaluation metrics (Sensitivity, Specificity, AUROC, AUPRC, Brier, etc.)

Given probability scores $\hat{p}_i$, define $\hat{y}_i = \mathbb{1}[\hat{p}_i \geq t]$.

- TP: predicted 1, true 1
- FP: predicted 1, true 0
- TN: predicted 0, true 0
- FN: predicted 1, true 1

Sensitivity / Recall / TPR

$$\text{Sensitivity} = P(\hat{y} = 1 \mid y = 1) = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

Specificity / TNR

$$\text{Specificity} = P(\hat{y} = 0 \mid y = 0) = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

FPR

$$\text{FPR} = 1 - \text{Specificity} = \frac{\text{FP}}{\text{FP} + \text{TN}}$$

Vary the threshold $t$from 1 down to 0.
At each t, compute $(\text{FPR}(t), \text{TPR}(t))$.
Plot TPR vs FPR.
AUROC is the area under that curve:

$$\text{AUROC} = \int_0^1 \text{TPR}(\text{FPR})\, d(\text{FPR})$$

In practice (discrete points), trapezoidal rule:

$$\text{AUROC} \approx \sum_{k=1}^{m-1} (\text{FPR}_{k+1} - \text{FPR}_k) \cdot \frac{\text{TPR}_{k+1} + \text{TPR}_k}{2}$$

At each threshold t:

$$\text{Precision}(t) = \frac{\text{TP}}{\text{TP} + \text{FP}}, \text{Recall}(t) = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

Plot Precision vs Recall.
AUPRC:

$$\text{AUPRC} = \int_0^1 \text{Precision}(\text{Recall})\, d(\text{Recall})$$

6.2. Oncology and Precision Medicine

The second area of clinical prediction over the past twenty years that has received ample attention is oncology, with major focus on cancer detection and therapeutic delivery methods. Machine learning methods built on pathology images, e.g., convolutional neural networks, are being used widely for detection, while risk models at the patient level are needed for treatment selection. For any cancer type, besides stage, other individual-specific risk indicators are needed for best treatment choice. Similar to cardiovascular applications, myriad such models have now emerged. Given the concern about induction of bias or treatment-theft in clinical risk models, prediction within stratification of patient sub-populations, based on a conventionally accepted clinical indicator, remains the most trusted approach for the day, even if that conventional predictor alone is insufficient for treatment selection.

Fairness of a proposed risk scoring model in the prediction of an oncological end-point outside the model-building cohort, represented by arguably the most important clinical development of the past two decades, also provides insight within this area. The recent rapid strides towards individualized patient-specific therapy in oncological domains, amply justified by differences in inherent and therapeutic responses among ethnic/racial groups, provide crucial timely domain-specific application-area differentiation. Recent model developments have now provided black-white routes or pathways to a large number of end-points in oncological scoring and therapy-determining contexts.

7. Challenges, Limitations, and Future Directions

Data-driven health-care solutions to improve health outcome and quality of life for individuals with wide socio-stratification range have become a trend. Yet, models built on only selected or isolated population constitute potential risks. The consequences of algorithmic bias due to disproportionate representation of certain demographic groups in health-care models may undermine their real-world interchangeability and generalizability. The awareness of fairness and equity across diverse populations continues. Moreover, rare-event prediction and extreme high-dimensional features (e.g., Oncology) may require special attention to model robustness against overfitting.

Whereas, Data reliability and compatibility are critical for the development of predictive algorithms. Lack of transportability has been identified as a main challenge toward ensuring model adoption across various clinical environments and increased real clinical value. Beyond standard external model validation for individual or multicentric studies, frameworks based on extreme validation set and hitters' hypothesis have been proposed.

Building on these concerns, contemporary research increasingly emphasizes the need for methodological frameworks that explicitly integrate fairness, robustness, and transportability into the lifecycle of data-driven health-care models. Rather than relying solely on conventional development pipelines optimized for overall accuracy, emerging approaches advocate for stratified performance assessment across demographic and clinical subgroups, incorporation of bias-mitigation strategies during training, and systematic stress-testing under distributional shifts. In parallel, advances in rare-event modeling and high-dimensional learning highlight the importance of regularization, representation learning, and uncertainty-aware methods to prevent overfitting and preserve clinical interpretability, particularly in complex domains such as oncology. Complementing standard external validation, extreme validation sets and hitters' hypothesis–driven frameworks offer promising avenues to probe model behavior in edge-case scenarios and heterogeneous settings, thereby providing deeper insight into failure modes and generalizability. Collectively, these efforts underscore a paradigm shift from building merely performant models toward developing trustworthy, equitable, and transportable predictive systems capable of delivering consistent real-world value across diverse clinical environments and populations.

Fig 4: Challenges, Limitations, and Future Directions

7.1. Data Bias, Fairness, and Equity

Significant advances in data collection have afforded unparalleled opportunities for personalized and precision medicine through extensive and diverse population-based healthcare data. Yet, the high-dimensional datasets employed in Big Data analysis may inherently lead to data bias. The size of the training cohort may act as a double-edged sword: on the one hand, a large cohort may contain more outliers, and on the other hand, a cohort that is orders of magnitude larger than the test cohort may not ensure generalization to the target population. While ML models have shown promise for improving prediction accuracy, they may inadvertently learn biases inadvertently encoded into the data, leading to questions of fairness and equity of risk prediction models: which groups of patients would be disadvantaged? Would the model be interpretable for high-stakes medical decision-making?

Unbiased representation of specific subpopulations, such as racial minorities and patients of a certain sex, in both training and test cohorts is essential for equitable clinical use. Some research has demonstrated that fair decision boundaries with respect to sensitive attributes can be learned, while other studies have investigated fairness-aware learning. Most of these approaches incorporate fairness constraints directly into the learning process via adversarial methods, discern performance across groups during model selection, and explicitly reduce the information about sensitive attributes in the features during representation learning. Statistical techniques have also been proposed to decrease data or decision bias while maintaining accuracy.

7.2. Robustness, Generalizability, and Reproducibility

The risk of overfitting with machine learning (ML) is a concern shared across many data domains. Yet in healthcare, prediction models trained on large amounts of patients and events often generalize well to external or new clinical settings, even in the absence of explicit regularization. That said, the transferability of ML models remains an open question, particularly when applied to subpopulations or healthcare systems with significantly different case mix, including socio-economic features. In such circumstances, demographic, economic, or ethnic imbalances may lead to disparities in care, such as in heart failure prediction, where deprivation indices were shown to be predictive in men but not in women.

Although cross-site validation is always preferable, a lack of external cohorts from independent sources can hinder assessment of a model's transportability. Nevertheless, ML can often help garner insights concerning distributional differences. Models used to assess risk in electrocardiograms, for instance, were shown to be incompletely invariant across age. Population-stratified models, defined using supervised clustering, provided both improvements to accuracy and increased interpretability, delineating clinically-relevant groups of ECG traces.

The growing popularity of autoML systems, while practical for exploratory endeavors, can compound issues of generalizability. Models generated by these platforms can be complex, feature-rich, and often lack interpretability or the capacity to convey clear clinical information. Moreover, when frequently adopted by non-experts simply to gain access to publishing venues, numerous papers may unwittingly instantiate a similar methodology to the same clinical risk or progression problem. In such circumstances, translational utility often becomes less about answering a specific question and more about simply obtaining yet another model for a particular disease.

8. CONCLUSION

Exponential improvements in digital storage, computational power, and connected devices have paved the way for the Big Data revolution. Healthcare, a cornerstone of modern economies, generates vast amounts of data in electronic Charlotte models, payers, pharmacies, clinics, and hospitals recording information about patients, test results, treatments, and costs. Although Big Data volumes have increased exponentially and their breadth has widened, they are still of limited use for clinical care, clinical risk prediction, and clinical decision support because predictive models are generally developed by a small number of specialized centers using traditional population-level datasets. It is essential to establish frameworks that harness Big Data–enabled artificial intelligence to make clinically applicable predictions more widely.

Risk models predict probabilities of onset of diseases or events in predetermined time horizons and are typically built using supervised statistical methods and represented in the form of scores or web portals accessible to medical professionals. Model performance is assessed using metrics adapted from information retrieval, and conclusions focus on internal, out-of-sample validation because real-word litmus tests are rare. Recent advances have made it possible to assess risk scoring in the Big Data context using modern ML methods, beginning with the construction of a framework that supports the construction of risk models from the ingesting, integrating, and storage of Big Data through representation learning and feature engineering.

8.1. Future Directions

With widespread Big Data availability, the growth of advanced computing architectures operating with the cloud, the maturation of ML methods and statistical frameworks appropriate for High-Dimensional Data

Problems, and the introduction of new paradigms enabling the crowd-sourcing of knowledge representation and modeling, Machine Learning and especially Deep Learning approaches have gained ground in many application areas. These advantages make them more promising for the prediction of difficult to model clinical events. Nevertheless, important challenges must still be addressed before this potential can be fully achieved. Healthcare decision-making should ultimately aim to provide health services to patients equitably and fairly while reducing health deprivations and disparities across population groupings. Empirical evidence suggests that unequal healthcare treatment and poorer clinical outcomes can be attributed to patient grouping based on some sensitive attributes such as sex, sexual identity, racial identity—especially in the USA, socioeconomic attributes, or prevalent clinical conditions among others.

Recent ML literature supports the claim that these same attributes can induce data biases that impact model fairness. Demographic considerations must therefore complement traditional performance evaluation measures. Decision support based on ML prediction of ordinal or categorical outcomes often leads clinicians and care-takers to classifying subjects in a single fragile class. Transportability of prediction models is often poor, with a model trained over one population not being able to yield reliable predictions on another, independently sampled, population and such generalization ability is not always easy to estimate. These issues are further aggravated by the use of external APIs and the creation of proprietary data lakes by tech giants. Addressing these concerns and presenting some recent solutions opens avenues for future research able to contribute towards a deeper understanding of ML prediction at large scale in medicine.

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