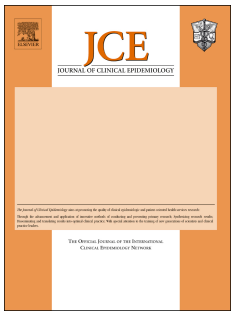

Systematic review identifies the design and methodological conduct of studies on machine learning-based prediction models

Constanza L. Andaur Navarro, doctoral student, Johanna AA. Damen, assistant professor, Maarten van Smeden, associate professor, Toshihiko Takada, assistant professor, Steven WJ. Nijman, doctoral student, Paula Dhiman, research fellow, Jie Ma, medical statistician, Gary S. Collins, professor, Ram Bajpai, research fellow, Richard D. Riley, professor, Karel GM. Moons, professor, Lotty Hooft, professor

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REVIEW

Systematic review identifies the design and methodological conduct of studies on machine learning-based prediction models

Constanza L Andaur Navarro[1,2] *doctoral student* (c.l.andaurnavarro@umcutrecht.nl, 0000-0002-7745-2887),
Johanna AA Damen[1,2] *assistant professor* (j.a.a.damen@umcutrecht.nl, 0000-0001-7401-4593),
Maarten van Smeden[1], associate professor (m.vansmeden@umcutrecht.nl, 0000-0002-5529-1541),
Toshihiko Takada[1] *assistant professor* (t.takada@umcutrecht.nl, 0000-0002-8032-6224),
Steven WJ Nijman[1] *doctoral student* (S.W.J.Nijman@umcutrecht.nl, 0000-0001-6798-2078),
Paula Dhiman[3,4] *research fellow* (paula.dhiman@ndorms.ox.ac.uk, 0000-0002-0989-0623),
Jie Ma[3] *medical statistician* (jie.ma@csm.ox.ac.uk, 0000-0002-3900-1903),
Gary S Collins[3,4] *professor* (gary.collins@csm.ox.ac.uk, 0000-0002-2772-2316),
Ram Bajpai[5] *research fellow* (r.bajpai@keele.ac.uk, 0000-0002-1227-2703),
Richard D Riley[5] *professor* (r.riley@keele.ac.uk, 0000-0001-8699-0735),
Karel GM Moons[1,2] *professor* (k.g.m.moons@umcutrecht.nl, 0000-0003-2118-004X),
Lotty Hooft[1,2] *professor* (l.hooft@umcutrecht.nl, 0000-0002-7950-2980)

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
[2]Cochrane Netherlands, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
[3]Center for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom.
[4]NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.
[5] Centre for Prognosis Research, School of Medicine, Keele University, Keele, United Kingdom.

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Correspondence to: Constanza L Andaur Navarro, c.l.andaurnavarro@umcutrecht.nl
Julius Centre for Health Sciences and Primary Care, Universiteitsweg 100, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands.

ABSTRACT

Objective. We sought to summarize the study design, modelling strategies, and performance measures reported in studies on clinical prediction models developed using machine learning techniques.

Study Design and Setting. We search PubMed for articles published between 01/01/2018 and 31/12/2019, describing the development or the development with external validation of a multivariable prediction model using any supervised machine learning technique. No restrictions were made based on study design, data source, or predicted patient-related health outcomes.

Results. We included 152 studies, 58 (38.2% [95%CI 30.8-46.1]) were diagnostic and 94 (61.8% [95%CI 53.9-69.2]) prognostic studies. Most studies reported only the development of prediction models (n=133, 87.5% [95%CI 81.3-91.8]), focused on binary outcomes (n=131, 86.2% [95%CI 79.8-90.8), and did not report a sample size calculation (n=125, 82.2% [95%CI 75.4-87.5]). The most common algorithms used were support vector machine (n=86/522, 16.5% [95%CI 13.5-19.9]) and random forest (n=73/522, 14% [95%CI 11.3-17.2]). Values for area under the Receiver Operating Characteristic curve ranged from 0.45 to 1.00. Calibration metrics were often missed (n=494/522, 94.6% [95%CI 92.4-96.3]).

Conclusions. Our review revealed that focus is required on handling of missing values, methods for internal validation, and reporting of calibration to improve the methodological conduct of studies on machine learning-based prediction models.

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Running title: Review on studies on ML-based prediction models

INTRODUCTION

Clinical prediction models aim to improve healthcare by providing timely information for shared decision-making between clinician and their patients, risk stratification, changes in behaviour, and to counsel patients and their relatives.[1] A prediction model can be defined as the (weighted) combination of several predictors to estimate the likelihood or probability of the presence or absence of a certain disease (diagnostic model), or the occurrence of an outcome over a time period (prognostic model).[2] Traditionally, prediction models were developed using regression techniques, such as logistic or time-to-event regression. However, in the past decade, the attention and use of machine learning approaches to developing clinical prediction models has rapidly grown.

Machine learning can be broadly defined as the use of computer systems that fit mathematical models that assume non-linear associations and complex interactions. Machine learning has a wide range of potential applications in different pathways of healthcare. For example, machine learning is applied in stratified medicine, triage tools, image-driven diagnosis, online consultations, medication management, and to mine electronic medical records.[3] Most of these applications make use of supervised machine learning whereby a model is fitted to learn the conditional distribution of the outcome given a set of predictors with little assumption on data distributions, non-linear associations, and interactions. This model can be later applied in other but related individuals to predict their (yet unknown) outcome. Support vector machines (SVM), random forests (RF), and neural networks (NN) are some examples of these techniques.[4]

The number of studies on prediction models published in the biomedical literature increases every year.[5,6] With more healthcare data being collected and increasing computational power, we expect studies on clinical prediction models based on (supervised) machine learning techniques to become even more popular. Although numerous models are being developed and validated for various outcomes, patients' populations, and healthcare settings, only a minority of these published models are successfully implemented in clinical practice.[7,8]

The use of appropriate study designs and prediction model strategies to develop or validate a prediction model could improve their transportability into clinical settings.[9] However, currently there is a dearth of information about which study designs, what modelling strategies, and which performance measures do studies on clinical prediction models report when choosing machine learning as modelling approach.[10–12] Therefore, our aim was to systematically review and summarise the characteristics on study design, modelling steps, and performance measures reported in studies of prediction models using supervised machine learning.

METHODS

We followed the PRISMA 2020 statement to report this systematic review.[13]

Eligibility criteria

We searched via PubMed (search date 19 December 2019) for articles published between 1 January 2018 and 31 December 2019 (Supplemental file 1). We focused on primary studies that described the development and/or validation of one or more multivariable diagnostic or prognostic prediction model(s) using any supervised machine learning technique. A multivariable prediction model was defined as a model aiming to predict a health outcome by using two or more predictors (features). We considered a study to be an instance of supervised machine learning when reporting a non-regression approach to model development. If a study reported machine learning models alongside regression-based models, this was included. We excluded studies reporting only regression-based approaches such as unpenalized regression (e.g., ordinary least squares or maximum likelihood logistic regression), or penalized regression (e.g., lasso, ridge, elastic net, or Firth's regression), regardless of whether they referred to them as machine learning. Any study design, data source, study population, predictor type or patient-related health outcome was considered.

We excluded studies investigating a single predictor, test, or biomarker. Similarly, studies using machine learning or AI to enhance the reading of images or signals, rather than predicting health outcomes in individuals, or studies that used only genetic traits or molecular ('omics') markers as predictors, were excluded. Furthermore, we also excluded reviews, meta-analyses, conference abstracts, and articles for which no full text was available via our institution. The selection was restricted to humans and English-language studies. Further details about eligibility criteria can be found in our protocol.[14]

Screening and selection process

Titles and abstracts were screened to identify potentially eligible studies by two independent reviewers from a group of seven (CLAN, TT, SWJN, PD, JM, RB, JAAD). After selection of potentially eligible studies, full text articles were retrieved and two independent researchers reviewed them for eligibility; one researcher (CLAN) screened all articles and six researchers (TT, SWJN, PD, JM, RB, JAAD) collectively screened the same articles for agreement. In case of any disagreement during screening and selection, a third reviewer was asked to read the article in question and resolve.

Extraction of data items

We selected several items from existing methodological guidelines for reporting and critical appraisal of prediction model studies to build our data extraction form (CHARMS, TRIPOD, PROBAST).[15–18] Per study, we extracted the following items: characteristics of study design (e.g.

cohort, case-control, randomized trial) and data source (e.g. routinely collected data, registries, administrative databases), study population, outcome, setting, prediction horizon, country, patient characteristics, sample size (before and after exclusion of participants), number of events, number of candidate and final predictors, handling of missing data, hyperparameter optimization, dataset splitting (e.g. train-validation-test), method for internal validation (e.g. bootstrapping, cross validation), number of models developed and/or validated, and availability of code, data and model. We defined country as the location of the first author's affiliation. Per model, we extracted information regarding the following items: type of algorithm used, selection of predictors, reporting of variable importance, penalization techniques, reporting of hyperparameters, and metrics of performance (e.g., discrimination and calibration).

Items were recorded by two independent reviewers. One reviewer (CLAN) recorded all items, whilst the other reviewers collectively assessed all articles (CLAN, TT, SWJN, PD, JM, RB, JAAD). Articles were assigned to reviewers in a random manner. To accomplish consistent data extraction, the standardized data extraction form was piloted by all reviewers on five articles. Discrepancies in data extraction were discussed and solved between the pair of reviewers. The full list of extracted items is available in our published protocol.[14]

We extracted information on a maximum number of 10 models per article. We selected the first 10 models reported in the methods section of articles and extracted items accordingly in the results section. For articles describing external validation or updating, we carried out a separate data extraction with similar items. If studies referred to the supplemental file for detailed descriptions, the items were checked in those files. Reviewers could also score an item as not applicable, not reported, or unclear.

Summary measures and synthesis of results

Results were summarized as percentages (with confidence intervals calculated using the Wilson score interval and the Wilson score continuity-corrected interval, when appropriated), medians, and interquartile range (IQR), alongside a narrative synthesis. The reported number of events was combined with the reported number of candidate predictors to calculate the number of events per variable (EPV). Data on a model's predictive performance was summarized for the apparent performance, corrected performance, and externally validated performance. We defined "apparent performance" when studies reported model performance assessed in the same dataset or sample in which the model was developed and in case no re-sampling methods were used; "corrected performance" when studies reported model performance assessed in test dataset and/or using re-sampling methods; and "externally validated performance" when studies reported model performance assessed in another sample than the one use for model development. As we wanted to identify the methodological conduct of studies on prediction models developed using machine learning, we did not evaluate the nuances of each modelling approach or its performance, instead

we kept our evaluations at study level. We did not perform a quantitative synthesis of the model' performance (i.e., meta-analysis), as this was beyond the scope of our review. Analysis and synthesis of data was presented overall. Analyses were performed using R (version 4.1.0, R Core Team, Vienna, Austria).

RESULTS

Among 24,814 articles retrieved, we drew a random sample of 2482 articles. After title and abstract screening, 312 references potentially met the eligibility criteria. After full-text screening, 152 articles were included in this review: 94 (61.8% [95%CI 53.9-69.2]) prognostic and 58 (38.2% [95%CI 30.8-46.1]) diagnostic prediction model studies (Figure 1). Detailed description of the included articles is provided in Supplemental file 2.

In 152 articles, 132 (86.8% [95%CI 80.5-91.3]) studies developed prediction models and evaluated their performance using an internal validation technique, 19 (12.5% [95%CI 8.2-18.7]) studies developed and externally validated the same ML based prediction model, and 1 (0.6%) study included model development with external validation of another comparative model (eventually included as development with internal validation). Eighty-seven studies (57% [95% CI 49.3-64.8]) were published in 2019 and 65/152 studies (42.8% [95% CI 35.2-50.7]) in 2018. The three clinical fields with the most articles were oncology (n=21/152, 13.8% [95%CI 9.2–20.2), surgery (n=20/152, 13.5% [95%CI 8.7-19.5), and neurology (n=20/152, 13.5% [95%CI 8.7-19.5]). Most articles originated from North America (n=59/152, 38.8% [95%CI 31.4-46.7]), followed by Asia (n=46/152, 30.3% [95%CI 23.5-38]) and Europe (n=37/152, 24,3% [95%CI 18.2-31.7]). Half of the studies had a first author with a clinical affiliation (n=85/152, 56% [95%CI 48-63.6]). Other characteristics are shown in Table 1.

Overall, 1,429 prediction models were developed (Median: 9.4 models per study, IQR: 2-8, Range: 1-156). As we set a limit on data extraction to 10 models per article, we evaluated 522 models. The most common applied modeling techniques were support vector machine (n=86/522, 16.5% [95%CI 13.5-20]), logistic regression (n=74/522, 14.2% [95%CI 11.4-17.5]), and random forest ([n=73/522, 14% [95%CI 11.2-17.3]). Further modelling algorithms are described in Table 2. In 120/152 (78.9% [95%CI 71.8-84.7]) articles, authors recommended at least one model usually based on model performance (i.e., AUC).

Participants

Participants included in the reviewed studies were mostly recruited from secondary (n=32/152, 21.1% [95%CI 15.3-28.2]) and tertiary care (n=78/152, 51.3% [95%CI 43.4-59.1]) settings (Table 1). Approximately half of the studies involved data from one center (n=73/152, 48% [95%CI 40.2-55.9]) (Table 3).

Data sources

The prediction models were most frequently developed using cohort data, either prospective (n=50/152, 32.9% [95%CI 25.9-40.7]) or retrospective (n=48/152, 31.6% [95%CI 24.7-39.3]). Electronic medical records were used in 30/152 studies (19.7% [95%CI 14.2-26.8]). Data collection was conducted on average for 41.9 months (IQR 3 to 60 months) when used to develop models, while for externally validation this was 44.4 months (IQR 1.75 to 42 months). In 101 out

of 152 studies (66.4% [95%CI 58.6-73.5]), the time horizon for the predictions was mostly unspecified. However, when reported (n=51/152, 33.6% [95%CI 26.5-41.4]), the time horizon of prediction ranged from 24 hours to 8 years (Table 3).

Outcome

Most models were developed to predict a binary outcome (n=131/152, 86.2% [95%CI 79.8-90.8]). The most frequent predicted outcome was complications after a certain treatment (n=66/152, 43.4% [95%CI 35.8-51.4]). Mortality was also a common endpoint (n=21/152, 13.8% [95%CI 9.2-20.2]) (Table 1).

Candidate predictors

Candidate predictors frequently involved demographics, such as age and sex (n=120/152, 78.9% [95%CI 71.8-84.7]), clinical history (n=111/152, 73% [95%CI 65.5-79.4]), and blood and urine parameters (n=63/152, 41.4% [95%CI 33.9-49.4]). When applicable, treatment modalities were also considered as predictors (n=36/116, 31.0% [95%CI 17.6-31]). Studies included a median of 24 candidate predictors (IQR 13 – 112). Most studies included continuous variables as candidate predictors (n=131/152, 86.2% [95%CI 79.8-90.8]). Whether continuous predictors were categorized during data preparation was often unclear (n=104/152, 68.4% [95%CI 60.7-75.3]) (Table 4).

Sample size

Studies had a median sample size of 587 participants (IQR 172 – 6328). The number of events across the studies had a median of 106 (IQR 50 – 364). Based on studies with available information (n=28/152, 18.4% [95%CI 13.1-25.3]), a median of 12.5 events per candidate predictors were used for model development (IQR 5.7 – 27.7) (Table 5). Most studies did not report a sample size calculation or justification for sample size (n=125/152, 82.2% [95%CI 75.4-87.5]). When sample size justification was provided, the most frequent rationale given was based on the size of existing/available data used (n=16/27, 59.3% [95%CI 40.7-75.5]) (Table 3).

Missing values

Missing values were an explicit exclusion criterion of participants in 56 studies (n=56/152, 36.8% [95%CI 29.6-44.7]). To handle missing values, complete-case analysis was the most common method (n=30/152, 19.7% [95%CI 14.2-26.8]). Other methods were median imputation (n=10/152, 6.6% [95%CI 3.6-11.7), multiple imputation (n=6/152, 3.9% [95%CI 1.9-8.3]) and k-nearest neighbor imputation (n=5/152, 3.3% [95%CI 1.4-7.5]). Further methods to handle missing values are presented in Table 6.

Class imbalance

In our sample, 27/152 (17.8% [95%CI 12.5-24.6]) studies applied at least one method to purportedly address class imbalance, that is – when one class of the outcome outnumbers the

other class (Table 7). The most applied technique was Synthetic Minority Over-sampling Technique (SMOTE), a method that combines oversampling the minority class with undersampling the majority class. [19,20]

Modelling algorithms

Tree-based methods were applied in 166/522 (31.8% [95%CI 27.9-36]) models with random forest being the most popular (n=73/522, 14% [95%CI 11.2-17.3]). Alongside machine learning algorithm, unpenalized regression methods (n=101/522, 19.3% [95%CI 16.1-23.1]), and particularly logistic regression (n=74/522, 14.2 [95%CI 11.4-17.5]) were often applied. Few studies reported models built with penalized regression (n=29/522, 5.6% [95%CI 3.8-8]). NNs (n=74/522, 14.2% [95%CI 11.4-17.5]) and Naïve Bayes (n=22/522, 4.2% [95%CI 2.7-6.4]) were also applied in our sample of articles.

Selection of predictors

The strategy to build models was unclear in 168 out of 522 models (32.2% [95%CI 28.2-36.4]). Most models reported a data-driven approach for model building (n=192/522, 36.8% [95%CI 32.7-41.1]). One study reported the use of recursive feature elimination for model building (n=3/522, 0.6% [95%CI 0.1-1.8]). Selection of candidate predictors based on univariable predictor–outcome associations was used in 27/522 (5.2% [95%CI 3.5-7.5]) of the models. Further details on modelling strategies are presented in Table 8. Of the three studies that reported time-to-event outcomes none reported how they dealt with censoring.

Variable importance and hyperparameters

Variable importance scores show insight into how much each variable contributed to the prediction model.[21] For 316/522 (60.5% [95%CI 56.2-64.7]) models, authors did not provide these scores, while in 115/522 (22% [95%CI 18.6-25.9]) models these scores were reported without specifying the methods applied to obtain such calculations (Table 8). When reported, the mean decrease in node impurity was the most popular method (n=31/522, 5.9% [95%CI 4.1-8.4]). Hyperparameters (including default settings) were reported in 160/552 (30.7% [95%CI 26.8-34.8]) models. Strategies for hyperparameter optimization were described in 44/152 studies (28.9% [95%CI 22.3-36.3]). The most common method reported was cross-validation (n=15/152) [9.9% [95%CI 6.1-15.6]. Nine studies (n=9/152, 5.9% [95%CI 3.1-10.9]) split their dataset into a validation set for hyperparameter tuning (Table 7).

Performance metrics

Most models used measures of the area under the Receiver Operating Characteristic curve (AUC/ROC or the concordance (c)-statistic) (n=358/522, 68.6% [95%CI 64.4-72.5]) to describe the discriminative ability of the model (Table 9). A variety of methods were used to describe the agreement between predictions and observations (i.e., calibration), the most frequent being a calibration plot (n=23/522, 4.4% [95%CI 2.9-6.6]), calibration slope (n=17/522, 3.3% [95%CI 2-

5.3]), and calibration intercept (n=16/522, 3.1% [95%CI 1.8-5]). However, for the large majority no calibration metrics were reported (n=494/522, 94.6% [95%CI 92.2-96.3]). Decision curve analysis was reported for two models (n=2/522, 0.4% [95%CI 0.1-1.5]).[22] We also found overall metrics such as classification accuracy (n=324/522, 62.1% [95%CI 57.8-66.2]) and F1-score (n=79/522, 15.1% [95%CI 12.2-18.6]).

Uncertainty quantification

In 53/152 (34.9% [95% CI 22.8-42.7]) studies, discrimination was reported without precision estimates (i.e., confidence intervals or standard errors). Likewise, 7/152 (4.6% [95%CI 2.2-9.2] studies reported model calibration without precision estimates.

Predictive performance

Most models achieved discriminative ability better than chance (i.e., AUC 0.5) with a median apparent AUC of 0.82 (IQR 0.75-0.90; range 0.45 to 1.00), while internally validated AUC was also 0.82 (IQR: 0.74-0.89; range 0.46 to 0.99). For external validation, the median AUC was 0.73 (IQR: 0.70-0.78, range: 0.51-0.88). For calibration and overall performance metrics, see Table 10.

Internal validation

In total, 86/152 studies (56.6% [95%CI 48.6-64.2]) internally validated their models, most often splitting the dataset into a training and test set. The train-test sets were often split randomly (n=49/86, 57% [95%CI 46.4-66.9]) and in a few studies a temporal (non-random) split was applied (n=9/86, 10.5% [95%CI 5.6-18.7]). The proportion of the data used for test sets ranged from 10% to 50% of the total dataset. Seventy studies also performed cross-validation (46.1% [95%CI 38.3-54]) with ten studies reporting nested cross-validation (6.6% [95%CI 3.6-11.7]). Out of five studies performing bootstrapping (n=5/152, 3.3% [95%CI 1.4-7.5]), one reported 250 iterations, three reported 1000 iterations and one did not report the number of iterations. For further details see Table 3.

External validation

Few studies (n=19/152, 12.5% [95%CI 8.2-18.7]) performed an external validation. Eleven studies (n=11/19, 57.9% [95%CI 36.3-76.9]) used data from independent cohorts and eight (n=8/19, 42.1% [95%CI 23.1-63.7]) used subcohorts within the main cohort to validate their developed models. From the independent cohorts, three studies (n=3/19, 15.8% [95%CI 5.5-37.6]) used data from a different country. Five studies (n=5/19, 26.3% [95%CI 11.8-48.8]) described an external validation based on temporal differences on the inclusion of participants. Seven studies (36.8% [95%CI 19.1-59]) reported differences and similarities in definitions between the development and validation data.

Model availability

Some studies shared their prediction model either as a web-calculator or worked example (n=31/152, 20.4% [95%CI 14.8-27.5]). Furthermore, in a minority of studies datasets and code were accessible through repositories, which were shared as supplemental material (n=18/152, 11.8% [95%CI 7.6-17.9]; n=13/152, 8.6% [95%CI 5.1-14.1]). Details in Table 1.

DISCUSSION

Principal findings

In this study, we evaluated the study design, data sources, modelling steps, and performance measures in studies on clinical prediction models using machine learning across. The methodology varied substantially between studies, including modelling algorithms, sample size, and performance measures reported. Unfortunately, longstanding deficiencies in reporting and methodological conduct previously seen in studies with a regression-based approach, were also extensively found in our sample of studies on machine learning models.[9,23]

The spectrum of supervised machine learning techniques is quite broad.[24,25] In this study, the most popular modelling algorithms were tree-based methods (RF in particular) and SVM. RF is an ensemble of random trees trained on bootstrapped sub-sets of the dataset.[26] On the other hand, SVM first map each data point into a feature space to then identify the hyperplane that separates the data items into two classes while maximizing the marginal distance for both classes and minimizing the classification errors.[27] Several studies also applied regression-based methods (LR in particular) as benchmark to compare against the predictive performance of machine learning-based models.

Various other well-known methodological issues in prediction model research need to be further discussed. Our reported estimate on EPV is likely to be overestimated given than we were unable to calculate it based on number of parameters, and instead we used only the number of candidate predictors. A simulation study concluded that modern modelling techniques such as SVM and RF might even require 10 times more events.[28] Hence, the sample size in most studies on prediction models using machine learning remains relatively low. Furthermore, splitting datasets persists as a method for internal validation (i.e., testing), reducing even more the actual sample size for model development and increasing the risk of overfitting.[29,30] Whilst AUC was a frequently reported metric to assess predictive performance, prediction calibration or prediction error was often overlooked.[31] Moreover, a quarter of studies in our sample corrected for class imbalance without reporting recalibration, although recent research has shown that correcting for class imbalance may lead to poor calibration and thus, prediction errors.[32] Finally, therapeutic interventions were rarely considered as predictors in the prognostic models, although these can affect the accuracy and transportability of models.[33]

Variable importance scores, tuning of hyperparameters, and data preparation (i.e., data pre-processing) are items closely related to machine learning prediction models. We found that most studies reporting variable importance scores did not specify the calculation method. Data preparation steps (i.e., data quality assessment, cleaning, transformation, reduction) were often not described in enough transparent detail. Complete-case analysis remains a popular method to handle missing values in machine learning based models. Detailed description and evaluation on

how missing values were handled in our included studies has been provided elsewhere.[34] Last, only one third of models reported their hyperparameters settings, which is needed for reproducibility purposes.

Comparison to previous studies

Regression methods were not our focus (as we did not define them to be machine learning methods), but other reviews including both approaches show similar issues with methodological conduct and reporting.[12,35–37] Missing data, sample size, calibration, and model availability remain largely neglected aspects.[7,12,37–40] A review looking at the trends of prediction models using electronic health records (EHR) observed an increase in the use of ensemble models from 6% to 19%.[41] Another detailed review on prediction models for hospital readmission shows that the use of algorithms such as SVM, RF, and NN increased from none to 38% over the last five years.[10] Methods to correct for class imbalance in datasets concerning EHR increased from 7% to 13%.[41]

Strengths and limitations of this study

In this comprehensive review, we summarized the study design, data sources, modelling strategies, and reported predictive performance in a large and diverse sample of studies on clinical prediction model studies. We focused on all types of studies on clinical prediction models rather than on a specific type of outcome, population, clinical specialty, or methodological aspect. We appraised studies published almost three years ago and thus, it is possible that further improvements might have raised. However, improvements in methodology and reporting are usually small and slow even when longer periods are considered.[42] Hence, we believe that the results presented in this comprehensive review still largely apply to the current situation of studies on machine learning-based prediction models. Given the limited sample, our findings can be considered a representative rather than exhaustive description of studies on machine learning models.

Our data extraction was restricted to what was reported in articles. Unfortunately, few articles reported the minimum information required by reporting guidelines, thereby hampering data-extraction.[23] Furthermore, terminology differed between papers. For example, the term ‘validation’ was often used to describe tuning, as well as testing (i.e., internal validation). An issue already observed by a previous review of studies on deep learning models.[43] This shows the need to harmonize the terminology for critical appraisal of machine learning models.[44] Our data extraction form was based mainly on the items and signaling questions from TRIPOD and PROBAST. Although both tools were primarily developed for studies on regression-based prediction models, most items and signaling questions were largely applicable for studies on machine learning-based models, as well.

Implication for researchers, editorial offices, and future research

In our sample, it is questionable whether studies ultimately aimed to improve clinical care.[45] Aim, clinical workflow, outcome format, prediction horizon, and clinically relevant performance metrics

received very little attention. The importance of applying optimal methodology and transparent reporting in studies on prediction models has been intensively and extensively stressed by guidelines and meta-epidemiological studies.[46–48] Researchers can benefit from TRIPOD and PROBAST, as these provide guidance on best practices for prediction model study design, conduct and reporting regardless of their modelling technique.[16,17,46,47] However, special attention is required on extending the recommendations to include areas such as data preparation, tunability, fairness, and data leakage. In this review, we have provided evidence on the use and reporting of methods to correct for class imbalance, data preparation, data splitting, and hyperparameter optimization. PROBAST-AI and TRIPOD-AI, both extensions to artificial intelligence (AI) or machine learning based prediction models are underway.[44,49] As machine learning continues to emerge as a relevant player in healthcare, we recommend researchers and editors to reinforce a minimum standard on methodological conduct and reporting to ensure further transportability.[16,17,46,47]

We identified that studies covering the general population (e.g., for personalized screening), primary care settings, and time-to-event outcomes are underrepresented in current research. Similarly, only a relatively small proportion of the studies evaluated (validated) their prediction model on a different dataset (i.e., external validation).[50] In addition, the poor availability of the developed models hampers further independent validation, an important step before their implementation in clinical practice. Sharing the code and ultimately the clinical prediction model is a fundamental step to create trustworthiness on AI and machine learning for clinical application.[51]

CONCLUSIONS

Our study provides a comprehensive overview of the applied study designs, data sources, modelling steps, and performance measures used. Special focus is required in areas such as handling of missing values, methods for internal validation, and reporting of calibration to improve the methodological conduct of studies on prediction models developed using machine learning techniques.

Registration and protocol

This review was registered in PROSPERO (CRD42019161764). The study protocol can be accessed in doi:10.1136/bmjopen-2020-038832.

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Competing interests

None

Availability of data, code, and other materials

Articles that support our findings are publicly available. Template data collection forms, detailed data extraction on all included studies, and analytical code are available upon reasonable request.

Supplemental Material

Supplemental file 1. Search strategy

Supplemental file 2. Characteristics and citation of included articles

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Authors' contributions

Constanza L. Andaur Navarro: Conceptualization, Methodology, Investigation, Data Curation, Formal analysis, Writing - original draft, Writing - review & editing; **Johanna A.A. Damen:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision; **Maarten van Smeden:** Conceptualization, Writing - review & editing; **Toshihiko Takada:** Investigation, Writing - review & editing. **Steven WJ Nijman:** Investigation, Writing - review & editing; **Paula Dhiman:** Conceptualization, Methodology, Investigation, Writing - review & editing; Jie Ma: Investigation, Writing - review & editing; **Gary S Collins:** Conceptualization, Methodology, Writing - review & editing; **Ram Bajpai**: Investigation, Writing - review & editing; **Richard D Riley:** Conceptualization, Methodology, Writing - review & editing; **Karel GM Moons:** Conceptualization, Methodology, Writing - review & editing, Supervision; **Lotty Hooft:** Conceptualization, Methodology, Writing - review & editing, Supervision

Ethical approval

Not required for this work.

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Figure 1. Flowchart of included studies

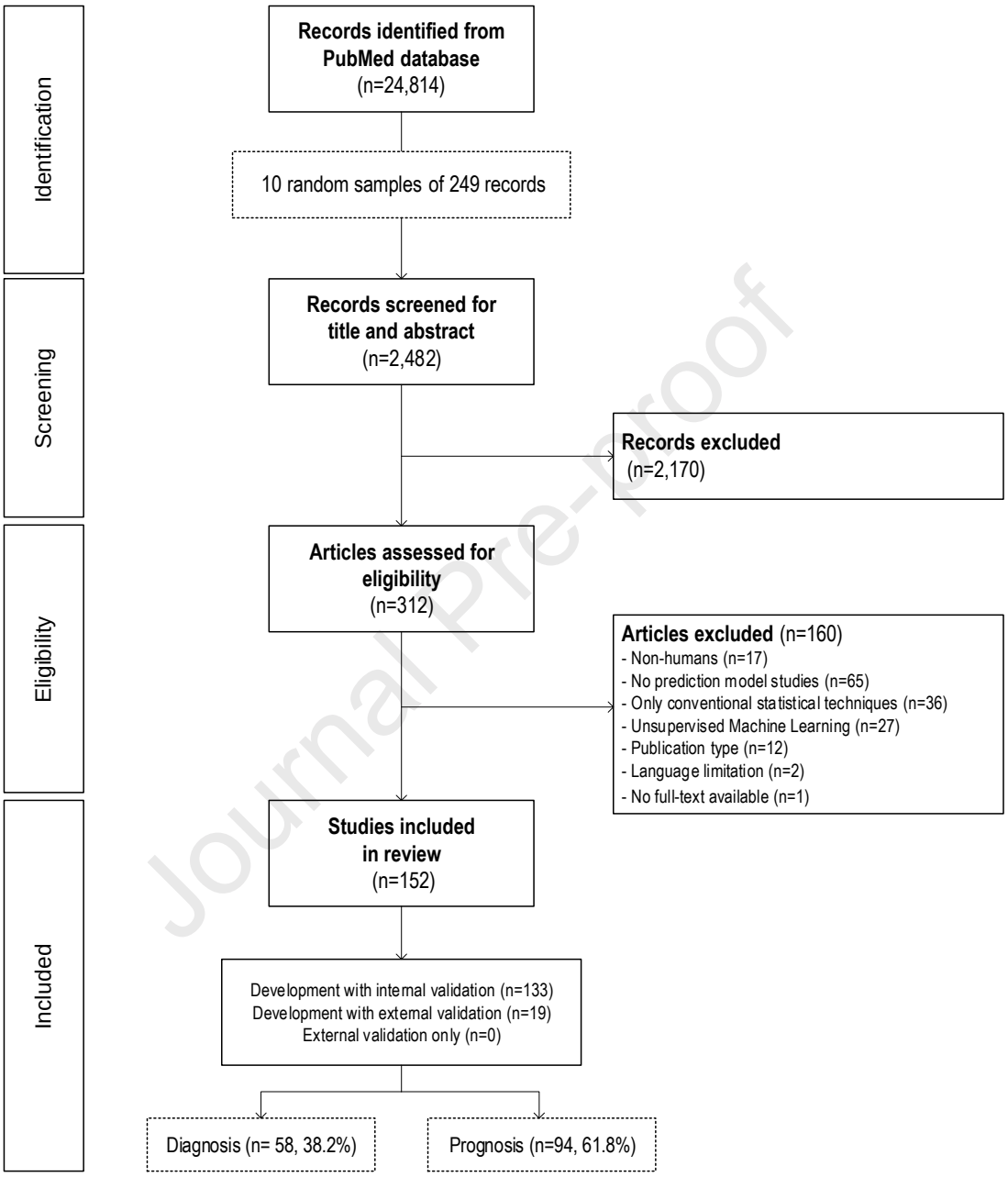

Table 1. General characteristics of included studies

	Total (n=152)
	n (%) [95% CI]
Study aim	
Diagnosis	58 (38.2) [30.8-46.1]
Prognosis	94 (61.8) [53.9-69.2]
Study type	
Model development only	133 (87.5) [81.3-91.8]
Model development with external validation	19 (12.5) [8.2-18.7]
Outcome aim	
Classification	120 (78.9) [71.8-84.7]
Risk probabilities	32 (21.0) [80.5-91.3]
Setting[†]	
General population	17 (11.2) [7.1-17.2]
Primary care	15 (9.9) [6.1-15.6]
Secondary care	32 (21.1) [15.3-28.2]
Tertiary care	78 (51.3) [43.4-59.1]
Unclear	13 (8.6) [5.1-14.1]
Outcome format	
Continuous	7 (4.6) [2.2-9.2]
Binary	131 (86.2) [79.8-90.8]
Multinomial	7 (4.6) [2.2-9.2]
Ordinal	2 (1.3) [0.4-4.7]
Time-to-event	3 (2.0) [0.7-5.6]
Count	2 (1.3) [0.4-4.7]
Type of outcome	
Death	21 (13.8) [9.2-20.2]
Complications	65 (42.8) [35.2-50.7]
Disease detection	30 (19.7) [14.2-26.8]
Disease recurrence	9 (5.9) [3.1-10.9]
Survival	3 (2.0) [0.7-5.6]
Readmission	4 (2.6) [1-6.6]
Other [a]	20 (13.2) [8.7-19.5]
Mentioning of reporting guidelines[†]	
TRIPOD	8 (5.3) [2.7-10]
STROBE	3 (2.0) [0.7-5.6]
Other [b]	5 (3.3) [1.4-7.5]
None	139 (91.4) [85.9-94.9]
Model availability[†]	
Repository for data	18 (11.8) [7.6-17.9]
Repository for code	13 (8.6) [5.1-14.1]
Model presentation [c]	31 (20.4) [14.8-27.5]
None	121 (79.6) [72.5-85.2]

[†] Counts are absolute numbers with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies reported more than one option.
[a] This includes length of stay, medication dose, patient's disposition, order type, lesion extension, laboratory results, cancer stage, treatment option, attendance, equipment usage, operative time.
[b] Guidelines for developing and reporting machine learning models in biomedical research (n=2), STARD (n=2), BRISQ (n=1).

[c] This includes simplified scoring rule, chart, nomogram, online calculator, or worked examples.

Table 2. Modelling algorithms for all extracted models

Modelling algorithm	All extracted models (n=522)
	n (%) [95%CI]
Unpenalized regression models	**101 (19.3) [16.1-23.1]**
Ordinary least squares regression [a]	27 (5.2) [3.5-7.5]
Maximum likelihood logistic regression	74 (14.2) [11.4-17.5]
Penalized regression models	**29 (5.6) [3.8-8]**
Elastic Net	9 (1.7) [0.8-3.4]
LASSO	13 (2.5) [1.4-4.3]
Ridge	7 (1.3) [0.6-2.9]
Tree-based models	**166 (31.8) [28-36]**
Decision trees (e.g., CART) [c]	46 (8.8) [6.6-11.7]
Random forest [d]	73 (14) [11.2-17.3]
Extremely randomized trees	1 (0.2) [0.01-1.2]
Regularized Greedy Forest	1 (0.2) [0.01-1.2]
Gradient boosting machine [e]	34 (6.5) [4.6-9.1]
XGBoost	11 (2.1) [1.1-3.9]
Neural Network (incl. deep learning) [b]	**75 (14.4) [11.5-17.7]**
Support Vector Machine	**86 (16.5) [13.5-20]**
Naïve Bayes	**22 (4.2) [2.7-6.4]**
K-nearest neighbor	**15 (2.9) [1.7-4.8]**
Superlearner ensembles	**14 (2.7) [1.5-4.6]**
Other [f]	**10 (1.9) [1-3.6]**
Unclear	**4 (0.8) [0.2-2.1]**

CART, Classification And Regression Tree; LASSO, Least Absolute Shrinkage and Selection Operator; XGBoost, extreme gradient boosting; CI, confidence interval.
[a] Discriminant analysis, generalized additive models (GAM), partial least squares were extracted as OLS regression.
[b] Multilayer perceptron, denseNet, convolutional, recurrent, and Bayesian neural networks were extracted as neural networks.
[c] This includes conditional inference tree (n=3), optimal tree (n=1).
[d] This includes Random Survival Forest (n=2).
[e] This includes lightGBM (n=1), adaBoost (n=8), catBoost (n=1), logitboost (n=1), RUSBoost (n=1), and stochastic (n=1).
[f] This includes bayesian network (n=3), rule-based classifier (n=1), highly predictive signatures (n=1), Kalman filtering (n=1), fuzzy soft set (n=1), adaptive neuro-fuzzy inference system (n=1), stochastic gradient descent (n=1), fully corrective binning (n=1).

Table 3. Study design of included studies, stratified by type of prediction model study

	Total (n=152)	Development only (n=133)	Development with external validation (n=19)
	n (%) [95%CI]	n (%) [95%CI]	n (%) [95%CI]
Data sources [†a]			
Prospective cohort	50 (32.9) [25.9-40.7]	43 (32.3) [25-40.7]	7 (36.8) [19.1-59]
Retrospective cohort	48 (31.6) [24.7-39.3]	45 (33.8) [26.3-42.2]	4 (21.1) [8.5-43.3]
Randomized Controlled Trial	3 (2.0) [0.7-5.6]	2 (1.5) [0.4-5.3]	1 (5.3) [0.3-24.6]
EMR	30 (19.7) [14.2-26.8]	28 (21.1) [15-28.7]	0
Registry	18 (11.8) [7.6-17.9]	15 (11.3) [7-17.8]	4 (21.1) [8.5-43.3]
Administrative claims	4 (2.6) [1-6.6]	4 (3.0) [1.2-7.5]	0
Case-control	18 (11.8) [7.6-17.9]	15 (11.3) [7-17.8]	3 (15.8) [5.5-37.6]
Number of centers	**110 (72.4)**	**98 (73.7)**	**12 (63.2)**
Median [IQR] (range)	1 [1-3], 1 to 51920	1 [1-3], 1 to 712	1 [1-10], 1 to 51920
Follow-up (months) [‡]	**47 (30.9)**	**39 (29.2)**	**8 (42.1)**
Median [IQR] (range)	41.9 [3-60], 0.3 to 307	43.6 [4.5-60], 0.3 to 307	33.5 [1.75-42], 1 to 144
Predictor horizon (months) [‡]	**49 (32.2) [25.3-40]**	**61 (45.9) [37.6-54.3]**	**7 (36.8)**
Median [IQR] (range)	8.5[1-36], 0.03 to 120	6 [1-33.5], 0.03 to 120	36 [6.5-60], 1 to 60
Sample size justification	**27 (17.8) [12.5-24.6]**	**24 (18.0) [12.4-25.4]**	**3 (15.8)**
Power	5 (18.5) [8.2-36.7]	5 (20.8) [9.2-40.5]	0
Justified time interval	5 (18.5) [8.2-36.7]	3 (12.5) [4.3-31]	2 (66.7)
Size of existing/available data	16 (59.3) [40.7-75.5]	15 (62.5) [42.7-78.8]	1 (33.3)
Events per variable	1 (3.7) [0.2-18.3]	1 (4.2) [0.2-20.2]	0
Internal validation[†]			
Split sample with test set	**86 (56.6) [48.6-64.2]**	NA	NA
(Random) split	49 (57) [46.4-66.9]		
(Non-random) split	9 (10.5) [5.6-18.7]		
Split [b]	28 (32.6) [23.6-43]		
Bootstrapping	**5 (3.3) [1.4-7.5]**	NA	NA
With test set	3 (60.0) [23.1-88.2]		
With cross-validation	1 (20) [1-62.4]		
Cross-validation	**70 (46.1) [38.3-54]**	NA	NA
Non-nested (single)	32 (45.7) [34.6]		
Nested	10 (14.3) [7.9-24.3]		
With test set	24 (34.3) [24.2-46]		
External validation[†]			
Chronological	NA	NA	5 (26.3) [11.8-48.8]
Geographical	NA	NA	3 (15.8) [5.5-37.6]
Independent dataset	NA	NA	11 (57.9) [36.3-76.9]
Fully independent dataset	NA	NA	8 (42.1) [23.1-63.7]

[†]Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies reported more than one measure. We report then the raw percentages. NA, not applicable.
[‡]We collected the longest follow-up and longest prediction horizon.
[a] Data sources also included surveys (n=2), cross-sectional studies (n=2).
[b] Unclear whether split sample was performed random or non-random.

Table 4. Predictors in included studies

	Total (n=152)
	n (%) [95% CI]
Type of candidate predictors†	
Demography	120 (78.9) [71.8-84.7]
Clinical history	111 (73.0) [65.5-79.4]
Physical examination	0
Blood or Urine parameters	63 (41.4) [33.9-49.4]
Imaging	49 (32.2) [52.3-40]
Genetic risk score	7 (4.6) [2.2-9.2]
Pathology	16 (10.5) [6.6-16.4]
Scale score	31 (20.4) [14.8-27.5]
Questionnaires	0
Treatment as candidate predictor	
Yes	36 (23.7) [17.6-31]
No	80 (52.6) [44.7-60.4]
Not applicable	36 (23.7) [17.6-31]
Continuous variables as candidate predictors	
Yes	131 (86.2) [79.8-90.8]
Unclear	17 (11.2) [7.1-17.2]
A-priori selection of candidate predictors‡	
Yes	63 (41.4) [33.9-49.4]
No	47 (30.9) [24.1-38.7]
Unclear	42 (27.6) [21.1-35.2]
Methods to handle continuous predictors†‡	
Linear (no change)	13 (8.6) [5.1-14.1]
Non-linear (planned)	2 (1.3) [0.4-4.7]
Non-linear (unplanned)	4 (2.6) [1-6.6]
Categorised (some)	16 (10.5) [6.6-16.4]
Categorised (all)	18 (11.8) [7.6-17.9]
Unclear	104 (68.4) [60.7-75.3]
Categorization of continuous predictors‡	
Data dependent	4 (2.6) [1-6.6]
No rationale	17 (11.2) [7.1-17.2]
Based on previous literature or standardization	13 (8.6) [5.1-14.1]
Not reported	118 (77.6) [70.4-83.5]

†Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies can report more than one measure.
‡As data preparation

Table 5. Sample size of included studies (n=152)

	Total (n=152)	
	n (%)	Median [IQR], range
Initial sample size	**93 (61.2)**	**999 [272-24522], 8 to 1093177**
External validation [a]	13 (68.4)	318 [90-682], 19 to 1113656
Final sample size	**151 (99.3)**	**587 [172-6328], 8 to 594751**
Model development	83 (54.6)	641 [226-10512], 5 to 392536
Internal validation [b]	83 (54.6)	230 [75-2892], 2 to 202215
External validation [a]	18 (94.7)	293 [71-1688], 19 to 59738
Initial number of events	**10 (6.6)**	**66 [15-207], 15 to 4370**
External validation [a]	1 (5.3)	107
Final number of events	**37 (24.3)**	**106 [50-364], 15 to 7543**
Model development	19 (13.2)	156 [47-353], 10 to 5054
Internal validation [b]	19 (13.2)	35 [26-109], 4 to 2489
External validation [a]	4 (21.1)	250 [121-990], 107 to 2834
Number of candidate predictors	119 (78.3)	24 [13-112], 2 to 39212
Number of included predictors	90 (59.2)	12 [7-23], 2 to 570
Events per candidate predictor [c]	28 (18.4)	12.5 [5.7-27.7], 1.2 to 754.3

[a] External validation was performed in 19 studies.
[b] Combines all internal validation methods, e.g., split sample, cross validation, bootstrapping.
[c] For model development.

Table 6. Handling of missing values, stratified by study type

	Total (n=152)	Development only (n=133)	Development with external validation (n=19)
	n (%) [95%CI]	n (%) [95%CI]	n (%) [95%CI]
Missingness as exclusion criteria for participants			
Yes	56 (36.8) [29.6-44.7]	51 (38.3) [30.5-46.8]	2 (10.5) [2.9-31.4]
Unclear	36 (23.7) [17.6-31]	33 (24.8) [18.2-32.8]	6 (31.6) [15.4-54]
Number of patients excluded	**36 (23.7) [17.6-31]**	**34 (25.6) [18.9-33.6]**	**0**
Median [IQR] (range)	191 [19-4209], 1 to 627180	224 [16-4699], 1 to 627180	0
Methods of handling missing data†			
No missing data	4 (2.6) [1-6.6]	3 (2.3) [0.8-6.4]	1 (5.3) [0.3-24.6]
No imputation	4 (2.6) [1-6.6]	4 (3) [1.2-7.5]	0
Complete case-analysis	30 (19.7) [14.2-26.8]	28 (21.1) [15-28.7]	2 (10.5) [2.9-31.4]
Mean imputation	4 (2.6) [1-6.6]	3 (2.3) [0.8-6.4]	1 (5.3) [0.3-24.6]
Median imputation	10 (6.6) [3.6-11.7]	10 (7.5) [4.1-13.3]	0
Multiple imputation	6 (3.9) [1.8-8.3]	6 (4.5) [2.1-9.5]	0
K-nearest neighbor imputation	5 (3.3) [1.4-7.5]	5 (3.8) [1.6-8.5]	0
Replacement with null value	3 (2.0) [0.7-5.6]	1 (0.8) [0-4.1]	2 (10.5) [2.9-31.4]
Last value carried forward	4 (2.6) [1-6.6]	4 (3) [1.2-7.5]	0
Surrogate variable	1 (0.7) [0-3.6]	1 (0.8) [0-4.1]	0
Random forest imputation	4 (2.6) [1-6.6]	3 (2.3) [0.8-6.4]	1 (5.3) [0.3-24.6]
Categorization	3 (2) [0.7-5.6]	2 (1.5) [0.4-5.3]	1 (5.3) [0.3-24.6]
Unclear	6 (3.9) [1.8-8.3]	5 (3.8) [1.6-8.5]	1 (5.3) [0.3-24.6]
Presentation of missing data			
Not summarized	129 (84.9) [78.3-89.7]	114 (85.7) [78.8-90.7]	16 (84.2) [62.4-94.5]
Overall	6 (3.9) [1.8-8.3]	4 (3) [1.2-7.5]	2 (10.5) [2.9-31.4]
By all final model variables	3 (2) [0.7-5.6]	3 (2.3) [0.8-6.4]	0
By all candidate predictors	13 (8.6) [5.1-14.1]	11 (8.3) [4.7-14.2]	1 (5.3) [0.3-24.6]
By number of variables	1 (0.7) [0-3.6]	1 (0.8) [0-4.1]	0

†Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies can report more than one technique.

Table 7. Machine learning aspects in the included studies

	Total (n=152)
	n (%) [95% CI]
Data preparation†	**58 (38.2) [30.8-46.1]**
Cleaning	21 (36.2) [25.1-49.1]
Aggregation	6 (10.3) [4.8-20.8]
Transformation	6 (10.3) [4.8-20.8]
Sampling	2 (3.4) [1-11.7]
Standardization/Scaling	11 (19) [10.9-30.9]
Normalization	22 (37.9) [26.6-50.8]
Integration	0
Reduction	12 (20.7) [12.3-32.8]
Other [a]	9 (15.5) [8.4-26.9]
Data splitting	**86 (56.6) [48.6-64.2]**
Train-test set	77 (50.7) [42.8-58.5]
Train-validation-test set	9 (5.9) [3.1-10.9]
Dimensionality reduction techniques	**9 (5.9) [3.1-10.9]**
CART	1 (11.1) [0.6-43.5]
Principal component analysis	3 (33.3) [12.1-64.6]
Factor analysis	1 (11.1) [0.6-43.5]
Image decomposition	1 (11.1) [0.6-43.5]
Class imbalance†	**27 (17.8) [12.5-24.6]**
Random undersampling	4 (14.8) [5.9-32.5]
Random oversampling	5 (18.5) [8.2-36.7]
SMOTE	11 (40.7) [24.5-59.3]
RUSBoost	1 (3.7) [0.2-18.3]
Other [b]	7 (25.9) [13.2-44.7]
Strategy for hyperparameter optimization†	**44 (28.9) [22.3-36.6]**
Grid search (no further details)	5 (3.3) [1.4-7.5]
Cross-validated grid search	14 (9.2) [5.6-14.9]
Randomized grid search	1 (0.7) [0-3.6]
Cross-validation	15 (9.9) [6.1-15.6]
Manual search	1(0.7) [0-3.6]
Pre-defined values/default	3 (2) [0.7-5.6]
Bayesian optimization	2 (1.3) [0.4-4.7]
Tree-structured parzen estimator method	1(0.7) [0-3.6]
Unclear	4 (2.6) [1-6.6]

†Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies can report more than one measure.
CART - Classification And Regression Tree.
[a] This includes matching, augmentation, noise filtering, merging, splitting, binning.
[b] This includes matching, resampling, class weighting, inverse class probability.

Table 8. Model building of all included studies

	Total (n=522)
	n (%) [95% CI]
Selection of predictors	
Stepwise	8 (1.5) [0.7-3.1]
Forward selection	31 (5.9) [4.1-8.4]
Backward selection	5 (1) [0.4-2.4]
All predictors	72 (13.8) [11-17.1]
All significant in univariable analysis	27 (5.2) [3.5-7.5]
Embedded in learning process	192 (36.8) [32.7-41.1]
Other	19 (3.6) [2.3-5.7]
Unclear	168 (32.2) [28.2-36.4]
Hyperparameter tunning reported	
Yes	160 (30.7) [26.7-34.8]
No	283 (54.2) [49.8-58.5]
Not applicable/Unclear	79 (15.1) [12.2-18.6]
Variable importance reported	
Mean decrease in accuracy	26 (5) [3.3-7.3]
Mean decrease in node impurity	31 (5.9) [4.1-8.4]
Weights/correlation	10 (1.9) [1-3.6]
Gain information	24 (4.6) [3-6.9]
Unclear method	115 (22) [18.6-25.9]
None	316 (60.5) [56.2-64.7]
Penalization methods used	
None	481 (92.1) [89.4-94.2]
Uniform shrinkage	3 (0.6) [0.1-1.8]
Penalised estimation	27 (5.2) [3.5-7.5]
Other	11 (2.1) [1.1-3.9]

Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies can report more than one measure.
[a] Both unpenalized and penalized regression models.
[b] Only for penalized regression techniques.

Table 9. Performance measures reported, stratified by model development and validation

	All extracted models (n=522)	
	n (%) [95% CI]	
	DEV	VAL
Calibration†		
Calibration plot	23 (4.4) [2.9-6.6]	1 (0.2) [0.01-1.2]
Calibration slope	17 (3.3) [2-5.3]	1 (0.2) [0.01-1.2]
Calibration intercept	16 (3.1) [1.8-5]	1 (0.2) [0.01-1.2]
Calibration in the large	1 (0.2) [0.01-1.2]	0
Calibration table	1 (0.2) [0.01-1.2]	0
Kappa	10 (1.9) [1-3.6]	0
Observed/expected ratio	1 (0.2) [0.01-1.2]	0
Homer-Lemeshow statistic	4 (0.8) [0.3-2.1]	0
None	494 (94.6) [92.3-96.3]	
Discrimination		
AUC/ AUC-ROC	349 (66.9) [62.6-70.9]	46 (8.8) [6.6-11.7]
C-statistic	9 (1.7) [0.8-3.4]	0
None	164 (31.4) [27.5-35.6]	
Classification †		
NRI	9 (1.7) [0.8-3.4]	0
Sensitivity/Recall	239 (45.8) [41.5-50.2]	30 (5.7) [4-8.2]
Specificity	193 (37) [32.8-41.3]	22 (4.2) [2.7-6.4]
Decision-analytic †		
Decision Curve Analysis	2 (0.4) [0.01-1.5]	0
IDI	1 (0.2) [0.01-1.2]	0
Overall †		
R2	14 (2.7) [1.5-4.6]	0
Brier score	19 (3.6) [2.3-5.7]	6 (1.1) [0.5-2.6]
Predictive values*	160 (30.7) [26.8-34.8]	10 (1.9) [1-3.6]
AUC difference	2 (0.4) [0.01-1.5]	0
Accuracy**	234 (44.8) [40.5-49.2]	26 (5) [3.4-7.3]
F1-score	79 (15.1) [12.2-18.6]	0
Mean square error	21 (4) [2.6-6.2]	0
Misclassification rate	9 (1.7) [0.8-3.4]	0
Mathew's correlation coefficient	5 (1) [0.4-2.4]	0
AUPR	21 (4) [2.6-6.2]	0

† Counts are absolute numbers, with column percentages in parentheses. The percentages sometimes do not add up to 100% because studies can report more than one performance measure.
*This includes models reporting positive predictive value as precision.
**This includes models reporting balance accuracy.
DEV, developed model; VAL, validation; AUC-ROC, area under the receiver operation characteristic curve; NRI, net reclassification index; IDI, integrated discrimination improvement; AUPR, area under the precision-recall curve; CI, confidence interval.

Table 10. Predictive performance of all extracted models*

	All extracted models (n=522)					
	Reported, n (%)	Apparent performance	Reported, n (%)	Corrected performance**	Reported, n (%)	Externally validated performance
		Median [IQR], range		Median [IQR], range		Median [IQR], range
Calibration						
Slope	11 (1.9)	1.05 [1.02 - 1.07], 0.53 to 1.46	15 (2.9)	1.3 [1-4], 0.52 to 17.6	4 (0.8)	9.9 [7.87-12.8], 5.7 to 17.6
Intercept	10 (1.9)	0.07 [0.05 - 0.12], -0.08 to 2.32	15 (2.9)	-0.01 [-1.85 - 0.15], -8.3 to 2.74	4 (0.8)	-4.5 [-5.7- -3.8], -8.3 to -3
Calibration-in-the-large	1 (0.2)	-0.008	0		0	
Observed:expected ratio	1 (0.2)	0.993	4 (0.8)	0.99 [0.98 - 1.01], 0.98 to 1.04	0	
Homer-Lemeshow	2 (0.2)	Not significant	0		0	
Pearson chi-square	1 (0.2)	Not significant	0		0	
Mean Calibration Error	4 (0.8)	0.81 [0.7 – 0.88], 0.51 to 0.99	0		0	
Discrimination						
AUC	249 (47.7)	0.82 [0.74-0.90], 0.45 to 1.00	154 (29.5)	0.82 [0.74-0.90], 0.46 to 0.99	46 (8.8)	0.82 [0.73-0.98], 0.52 to 0.97
Accuracy						
	128 (24.5)	79.8 [72.6-89.8], 44.2 to 100	117 (22.4)	81.4 [76-89.9], 17.8 to 97.5	9 (1.7)	70 [64-87], 55 to 90
Sensitivity						
	156 (29.9)	74 [58.6-87.8], 0 to 100	103 (19.7)	80 [66.3-89.7], 14.8 to 100	12 (2.3)	77.5 [63.9-83.5], 0.7 to 91
Specificity						
	122 (23.4)	82.2 [73.3-89.7], 17 to 100	80 (15.3)	83.2 [73.6-90.8], 46.6 to 100	10 (1.9)	74.4 [64.8-86.7], 42 to 90.5

* Counts are absolute numbers with column percentages in parentheses. The percentages sometimes do not add up to 100% because some studies did not report performance measure for all models pre-specified.
**We considered corrected performance only when authors stated results as such. Otherwise, performance measures were considered apparent performance by default.

What is new?

Key Findings

- Design and methodological conduct of studies on clinical prediction models based on machine learning vary substantially.

What this adds to what was known?

- Studies on clinical prediction models based on machine learning suffered from poor methodology and reporting similar to studies using regression approaches.

What is the implication and what should change now?

- Methodologies for model development and validation should be more carefully designed and reported to avoid research waste.
- More attention is needed to missing data, internal validation procedures, and calibration.
- Methodological guidance for studies on prediction models based on machine learning techniques is urgently needed.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Authors' contributions

Constanza L. Andaur Navarro: Conceptualization, Methodology, Investigation, Data Curation, Formal analysis, Writing - original draft, Writing - review & editing; **Johanna A.A. Damen:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision; **Maarten van Smeden:** Conceptualization, Writing - review & editing; **Toshihiko Takada:** Investigation, Writing - review & editing. **Steven WJ Nijman:** Investigation, Writing - review & editing; **Paula Dhiman:** Conceptualization, Methodology, Investigation, Writing - review & editing; Jie Ma: Investigation, Writing - review & editing; **Gary S Collins:** Conceptualization, Methodology, Writing - review & editing; **Ram Bajpai**: Investigation, Writing - review & editing; **Richard D Riley:** Conceptualization, Methodology, Writing - review & editing; **Karel GM Moons:** Conceptualization, Methodology, Writing - review & editing, Supervision; **Lotty Hooft:** Conceptualization, Methodology, Writing - review & editing, Supervision