A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models

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Word count: 3199

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Abstract

Objective: To compare performance of logistic regression (LR) with machine learning (ML) for clinical prediction modeling. Study design and setting: We conducted a Medline literature search (1/2016 to 8/2017), and extracted comparisons between LR and ML models for binary outcomes. Results: We included 71 out of 927 studies. The median sample size was 1250 (range 72-3,994,872), with 19 predictors considered (range 5-563) and 8 events per predictor (range 0.3-6,697). The most common ML methods were classification trees (30 studies), random forests (28), artificial neural networks (26), and support vector machines (24). Sixty-four (90%) studies used the area under the receiver operating characteristic curve (AUC) to assess discrimination. Calibration was not addressed in 56 (79%) studies. We identified 282 comparisons between a LR and ML model (AUC range, 0.52-0.99). For 145 comparisons at low risk of bias, the difference in logit(AUC) between LR and ML was 0.00 (95% confidence interval, -0.18 to 0.18). For 137 comparisons at high risk of bias, logit(AUC) was 0.34 (0.20 to 0.47) higher for ML. Conclusions: We found no evidence of superior performance of ML over LR for clinical prediction modeling, but improvements in methodology and reporting are needed for studies that compare modeling algorithms.

Key words:

Clinical prediction models; logistic regression; machine learning; AUC; calibration; reporting

What is new

Key Findings

- Studies comparing clinical prediction models based on logistic regression and machine learning algorithms suffered from poor methodology and reporting, in particular with respect to the validation procedure
- The studies rarely assessed whether risk predictions are reliable (calibration), but the area under the ROC curve (AUC) was almost always provided
- The AUC of logistic regression and machine learning models for clinical risk prediction were similar when fair comparisons were made; ML performance was higher in comparisons that were at high risk of bias

What this adds to what is known

- Machine learning models do not automatically lead to improved performance over traditional methods
- Model validation procedures are often not sound or not well reported, which hampers a fair model comparison in real world case studies

What should change now

- More attention for calibration performance of regression and machine learning models is urgently needed
- Model development and validation methodologies should be more carefully designed and reported to avoid research waste
- Research should focus more on identifying which algorithms have optimal performance for different types of prediction problems

1. Introduction

Clinical risk prediction models are ubiquitous in many medical domains. These models aim to predict a clinically relevant outcome using person-level information. The traditional approach to develop these models involves the use of regression models, for example logistic regression (LR) to predict disease presence (diagnosis) or disease outcomes (prognosis) [1]. Machine learning (ML) algorithms are gaining in popularity as an alternative approach for prediction and classification problems. ML methods include artificial neural networks, support vector machines, and random forests [2]. Whilst ML methods have been sporadically used for clinical prediction for some time [3,4], the growing availability of increasingly large, voluminous and rich datasets such as electronic health records data has reignited interest in exploiting these methods [5–7].

Definitions of what constitutes ML and the differences with statistical modeling have been discussed at length in the literature [8], yet the distinction is not clear-cut [9]. The seminal reference on this issue is Breiman's review of the 'two cultures' [8]. Breiman contrasts theory-based models such as regression with empirical algorithms such as decision trees, artificial neural networks, support vector machines, or random forests. A useful definition of ML is that it focuses on models that directly and automatically learn from data [10]. In contrast, regression models are based on theory and assumptions, and benefit from human intervention and subject knowledge for model specification. For example, ML performs modeling more automatically than regression regarding the inclusion of nonlinear associations and interaction terms [11]. To do so, ML algorithms are often highly flexible algorithms that require penalization to avoid overfitting, i.e. that predictions generalize poorly to new data [12]. Some researchers describe the distinction between statistical modeling and machine learning as a continuum [5]. Other researchers label any method that deviates from basic regression models as ML [13], such as penalized regression (e.g., LASSO, elastic net) or generalized additive models (GAM). We note that these methods do not belong to ML using the 'automatic learning from data' definition, and did not classify these as ML in this study.

Due to its flexibility, ML is claimed to have better performance over traditional statistical modeling, and to better handle a larger number of potential predictors [5–7,12,14–16]. However, recent research suggested that ML requires more data than LR, which contradicts the above claim [17]. Further, ML models are typically assessed in terms of discrimination performance (e.g. accuracy, area under the ROC curve), whilst the reliability of risk predictions (calibration) is often not assessed [18]. The claim of improved performance in clinical prediction is therefore not established.

The primary objective of this study was to compare the performance of LR with ML algorithms for the development of diagnostic or prognostic clinical prediction models for binary outcomes based on clinical data. Secondary objectives were to describe the characteristics of the studies, the type of ML algorithms that were used, the validation process , the modeling aspects of LR and ML, reporting quality, and risk of bias for comparing performance between regression and ML [19].

2. Materials and methods

The study was registered with PROSPERO (CRD42018068587). We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement.

2.1. Identification of studies

We searched MEDLINE on August 8th, 2017. We performed a sensitive literature search by using a broad working definition of ML (see the search string in Appendix A). We focused on articles published since 2016 (between January 1st, 2016 and August 8th, 2017) in order to base our analysis on recent studies.

2.2. Selection of studies

All abstracts were independently screened by two reviewers (EC, JM), conflicts were resolved by a third reviewer (BVC or JYV). The full text of selected abstracts were independently assessed for eligibility by three reviewers (EC, JM, BVC), and conflicts were resolved by consensus.

2.3. Inclusion and exclusion criteria

Studies were eligible if the article:

- Described the development of a diagnostic or prognostic prediction model for individualized prediction using two or more predictors
- Compared prediction models based on LR and ML algorithms

Studies were excluded if:

- A new modeling approach was introduced (hence a methodological focus) [20,21]
- Models were developed for non-humans
- The models made predictions for individual images or signals rather than participants
- Models were developed based on high-dimensional data modalities
- The primary interest was assessing risk factors rather than prediction modeling
- They were reviews of the literature
- Studies for which we were unable to obtain the full text

2.4. Data extraction and risk of bias

We focused on methodological issues of model development, and aspects that compromise the comparison of model performance between LR and ML algorithms. The list of extraction items was based on the CHARMS checklist and the QUADAS risk of bias tool and refined after extensive discussion among the authors [9,22]. The extracted items included general study characteristics, applied algorithms and their characteristics, data-driven variable selection, and model performance (Table A.1, Appendix B) [1,2,13,23–25].

From each article, we defined five signaling items to indicate potential bias. We elaborate on these items in Table A.2:

(1) unclear or biased validation of model performance
(2) difference in whether data-driven variable selection was performed (yes/no) prior to applying LR and ML algorithms
(3) difference in handling of continuous variables prior to applying LR and ML algorithms
(4) different predictors considered for LR and ML algorithms
(5) whether corrections for imbalanced outcomes where used only for LR or only for ML algorithms

Most papers developed several LR and/or ML models. These papers contain multiple comparisons between LR and ML algorithms, and we evaluated the signaling items per comparison. Each bias item was scored as no (not present), unclear, or yes (present). We considered a comparison at low risk of bias if the answer was ‘no’ for all five signaling items. If the answer was ‘unclear’ or ‘yes’ for at least one item, we assumed high risk of bias. We also summarized the signaling items for each study as a whole, by noting the worst case (no, unclear, yes) across all comparisons in the study.

2.5. Data analysis

We used descriptive statistics to summarize results. Within each paper, we identified all comparisons between LR and ML methods (see Appendix C). We identified multiple comparisons within the same paper as a result of implementing multiple ML algorithms, developing models for more than one outcome, developing models based on different predictor sets (e.g. once with and once without lab measurements), or developing models for several subgroups separately. Although the search string contrasted standard LR with penalized methods, we consider penalized LR (e.g. lasso, ridge, elastic net) to be LR rather than ML. Some papers contrasted LR with algorithms that are traditional statistical methods, such as discriminant analysis, Poisson regression, generalized estimating equations, and GAM. We did not classify these algorithms as ML. We compared the LR and ML models using the difference in the area under the ROC curve (AUC). We used AUC values in the following order of priority: external validation, internal validation, training data (no validation). Based on the extracted data, we classified ML algorithms into five broad groups: single classification trees, random forests, artificial neural networks, support vector machines, and other algorithms. We analyzed AUC differences for all comparisons, and with stratification for risk of bias. We performed a meta-regression of the difference between logit-transformed AUC using a random effect model to take clustering of comparisons by paper into account, and weighted by the square root of the validation sample size. Logit(AUC) was used to circumvent the bounded nature of the AUC [26].

3. Results

Our search identified 927 articles published since between 1/2016 and 8/2017, of which 802 studies were excluded based on title or abstract (Figure 1). 54 studies were excluded during full text screening. Seventy-one studies met inclusion criteria and came from a wide variety of clinical domains, with oncology and cardiovascular medicine as the most common (Table A.3-4) [27–97]

3.1. General study characteristics

The most common designs were cohort (n=39, 55%) and cross-sectional (n=18, 25%) (Table A.5). Overall, 50 studies (70%) focused on prognostic outcomes, 19 (27%) on diagnostic outcomes, and

two on both. The majority of studies (n=64, 90%) used existing data, and 27 (38%) used hospital-based multicenter data. The median number of centers was 5 (range 2-1,137) (Table A.6).

The median total sample size was 1,250 (range 72-3,994,872), median number of considered predictors was 19 (range, 5-563). 102 outcomes were considered in the 71 articles, the median event rate was 0.18 (range 0.002-0.50). We defined the number of events as the number of participants in the smallest outcome category. Nine articles developed models to predict more than one outcome. The median number of events per predictor in the training data was 8 (range 0.3-6,697) (Figure A.1).

Information on handling of missing data was lacking or unclear in 32 studies (45%) (Tables A.7-8). Sixteen studies (23%) performed a complete case analysis, 14 (20%) relied on ad hoc methods (mean imputation, missing indicator methods, variable deletion), and nine (11%) used single or multiple stochastic imputation, albeit poorly documented.

3.2. Overview of algorithms

Sixty-four studies used standard (maximum likelihood) LR, of which nine also used penalized LR (lasso, ridge, or elastic net) and one also used boosted LR (Table 1 and A.9). Six studies used only penalized LR, and 1 study used only bagged LR (classified as ML).

Forty-three studies used more than one ML algorithm. The most popular algorithms were classification trees (n=30, 42%), random forests (28, 39%), artificial neural networks (26, 37%), and support vector machines (24, 34%). Of 26 studies using artificial neural networks, 22 used 1 hidden layer, 3 used multiple hidden layers, and for 1 study this was unclear (Table A.9). When support vector machines were used, the Gaussian ('radial basis function') kernel was most often used (n=10).

3.3. Model development

Irrespective of algorithm (LR vs ML), 14 studies (20%) were not clear about how continuous variables were handled during model development (Table A.10). Discretization (into two or more categories) was used for some or all algorithms in 18 studies (25%), whereas continuous modeling was observed in 37 studies (52%), although this was often not explicitly stated. Data-driven variable selection before any model fitting was reported for 41 studies (58%).

Specifically for LR, handling of continuous predictors was unclear in 47/71 studies (66%). In 33/47, some or all predictors were kept continuous but it was unclear whether nonlinear associations were examined. For one study, it was clear that continuous variables were assumed to have linear

associations with the outcome. Discretization of some or all continuous predictors was carried out in 20 studies (28%), whereas nonlinearity was investigated in seven studies (10%). Sixty-three studies (89%) did not explicitly mention whether interaction effects were considered for LR models. The remaining eight studies were often unclear on the approach for interaction terms (Table A.11).

Penalized LR as well as many ML algorithms contain hyperparameters that determine the complexity/flexibility of the model. For the most commonly used algorithms, we observed that the approach for determining the hyperparameters was not clear in at least half of the studies (Table A.12). It was either unclear whether hyperparameters were tuned or default settings were used, or hyperparameters were said to be tuned but the tuning procedure was not clear.

3.4. Model validation

29 studies (41%) used a single random split of the data into train-test or train-validate-test parts (Table 2). Twenty-five studies used resampling (35%; 15 used cross-validation, 9 used repeated random splitting, and 1 used bootstrapping). Seven studies (10%) used some form of external validation, most commonly using a chronological split of data into training and test parts. Seven studies (10%) did not validate performance, and for three studies (4%) the approach depended on the algorithm. Importantly, in 48 studies (68%) we observed unclear reporting or potential biases in validation procedures for one or more algorithms. Common reasons were that hyperparameters were tuned or variable selection was done on all data (or this was not clearly specified), or that not all modeling steps were repeated when resampling was used for validation (Table A.13).

The AUC was the most commonly reported performance measure (64 studies, 90%), followed by sensitivity (45, 63%) and specificity (43, 61%) (Table A.14). Calibration performance was not discussed in 56 studies (79%) (Table A.15). Most commonly, calibration was addressed using grouped calibration plots (n=7). Only 1 study (1%) evaluated performance in terms of clinical utility using decision curve analysis.

In 21 studies, methods were applied to address outcome imbalance, i.e. an event rate far from 50% (Table A.16, see Discussion).

3.5. Comparison between performance of LR and ML

The most problematic risk of bias item was an unclear/biased validation procedure (Figure 2, Table A.17).

We identified 282 comparisons between standard/penalized LR (AUC 0.52-0.97) and ML models (AUC 0.58-0.99) in 58 papers. Of the remaining 13 papers, 7 did not report AUCs, 3 reported AUCs for some algorithms only, 1 reported AUCs to one decimal, 1 only applied standard and penalized LR, and 1 only applied bagged LR and random forests. 145 comparisons (51%) were labeled as having low risk of bias. The logit(AUC) was on average 0.25 higher for ML vs LR (95% CI 0.12 to 0.38) (Figures 3-4). However, the logit(AUC) difference was on average 0.00 (-0.18 to 0.18) for comparisons with low risk of bias, and 0.34 higher (0.20 to 0.47) for comparisons with high risk of bias. Trees uniformly had worse performance than other ML algorithms. Otherwise, results for different ML algorithms were similar.

Finally, Table A.18 reports on additional findings on methodology and reporting that could not be discussed in the main text due to space limitations.

4. Discussion

Our systematic review of studies that compare clinical prediction models using LR and ML yielded the following key findings. Reporting of methodology and findings was very often incomplete and unclear, model validation procedures still often were poor. Calibration of risk predictions was seldom examined, and AUC performance of LR and ML was on average no different when comparisons had low risk of bias. The latter finding is in line with the claim that traditional approaches often perform remarkably well [21].

Our findings lead to the following recommendations (Table A.19). First, fully report on all modeling steps and analyses in sufficient detail to maximize transparency and reproducibility. We recommend to adhere to the TRIPOD guidelines [19]. If necessary, include detailed descriptions as supplementary material. For complex procedures, a comprehensive flowchart of the development and validation procedures can be insightful - some studies provided this [53]. Second, if model validation is based on resampling, the model development should be based on all available data, and the resampling should then include all modelling steps that were used to build the model in order to estimate performance. Model development on all data was often not done. In addition, provide all information on these models to allow independent validation. Third, report training and test performance. The difference between these results is informative. Fourth, evaluate model performance in terms of calibration (whether risk estimates are accurate) and clinical utility for

decision making [18]. Preferably, calibration should be investigated using calibration curves, whereas the Hosmer-Lemeshow test should be avoided [18,98,99]. Clinical utility can be assessed using decision curve analysis, which is increasingly used in medical applications [100].

We found several differences between the ML and statistical literature. In the ML literature, calibration often refers to the transformation of non-probabilistic model outcomes into probabilities [101]. In this paper, calibration refers to the evaluation of the reliability of probabilistic (risk) estimates [18]. A transformation of model outcomes into probabilities is part of model development. Further, the ML literature has paid attention to the utility of models. For example cost curves are very similar to decision curve analysis [102]. Finally, the issue of class imbalance is common in the ML literature [13]. This is motivated by a dominant focus on classification and overall accuracy based on a 50% risk cut-off. However, adjusting class imbalance distorts prevalence and yields inadequate risk predictions. This is not acceptable for clinical risk prediction. In particular, downsampling is inefficient because it reduces sample size. Recent research clearly indicated that this increases the risk of overfitting [103].

The comparison of AUC performance between LR and ML depends on how one defines risk of bias and ML. We used five signaling items to consider comparisons as at low or high risk of bias. These items did not address whether LR models were penalized or included nonlinear and/or interaction effects. Regression is sometimes presented as a method that simply assumes linearity and additivity [7,104]. In comparison studies it is usually implemented as such, for example in two recent benchmark studies using dataset repositories [105,106]. Some criticize that assuming linearity and additivity will reduce the performance of regression, although this may depend on sample size. Regarding the definition of ML, we used a broad approach: we focused on alternative algorithms for LR, hereby only excluding classical statistical algorithms (we also excluded GAMs, although some may see this as an ML method). The rationale is that LR has been the standard method for clinical prediction, and more modern approaches are often discussed in relation to LR [6,7,14-17,104,107].

Future research should focus more on delineating the type of predictive problems in which various algorithms have maximal value. For example, the signal-to-noise ratio may be an important aspect in determining how successful ML will be [2,21,107]. ML tends to work well for problems with a strong signal-to-noise ratio [108], e.g. handwriting recognition, gaming, or electric load forecasting. Clinical prediction problems often have a poor signal-to-noise ratio [107] .

A limitation of our study is that it does not investigate which factors influence the difference in performance (e.g. sample size, number of predictors, hyperparameter tuning). We feel that such a study would be relevant, but should be performed by comparing different scenarios on the same

datasets to avoid confounding [106]. Another limitation is that many studies had a fairly limited number of events per considered predictor, a common problem despite repeated warnings [1,17,99,103,109]. This issue urgently needs better consideration. Some researchers claim that ML will not outperform LR when only a limited set of pre-specified predictors is considered, and that the advantage of ML lies in better handling a huge amount of predictors [3,7,12,15,16,104]. Unfortunately, all 23 comparisons that we identified from the seven included studies with >100 predictors were at high risk of bias. Nevertheless, their median AUC difference was -0.005. In contradiction with the above claim, recent research suggests that ML requires more data than LR [17]. A final limitation is that conducting a decent and detailed systematic review on this broad topic was time-consuming. In the meantime, new studies will have been published. Although there is the potential that methodology and reporting has improved, such improvements are slow even when longer time periods are considered [110–112].

In conclusion, evidence is lacking to support the claim that clinical prediction models based on ML lead to better AUCs than clinical prediction models based on LR. Reporting of papers that compare both types of algorithms needs to improve. Correct validation procedures are needed [113], with assessment of calibration and clinical utility in addition to discrimination, to define situations where modern methods have advantages over traditional approaches.

Acknowledgements

Funding source: This work was supported by by the Research Foundation – Flanders (FWO) [grant G0B4716N]; Internal Funds KU Leuven [grant C24/15/037]; Cancer Research UK [grant 5529/A16895]; the NIHR Biomedical Research Centre, Oxford, UK. The funding sources had no role in the conception, design, data collection, analysis, or reporting of this study.

Authors' contributions: E.C. was involved in the conception of the study, data collection, data analysis and interpretation, drafting of the article, and gave her final approval of the version to be published. J.M. was involved in data collection, critical revision of the article, and gave her final approval of the version to be published. G.S.C. was involved in the conception of the study, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. E.W.S. was involved in the conception of the study, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. J.Y.V. was involved in the conception of the study, data collection, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. B.V.C. was involved in the conception of the study, data collection, data analysis and interpretation, drafting of the article, and gave his final approval of the version to be published.

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Table 1. Algorithms used in the studies (n=71 studies). Counts refer to papers, e.g. if one paper applies several types of classification trees, this is counted only once.

Type of algorithm	**N (%)**
Logistic regression (LR) methods	71 (100%)
Standard LR only	54
Standard and penalized LR	9
Penalized LR only	6
Standard LR and boosted LR	1
Bagged LR	1
Alternative machine learning methods	
Classification tree (e.g. CART, C4.5)	30 (42%)
Random forest (RF)	28 (39%)
Support vector machine (SVM)	24 (34%)
Artificial neural network (ANN)	26 (37%)
Other algorithms	30 (42%)
Boosted tree methods (e.g. gradient boosting machines)	16
Naïve Bayes	9
Ensemble of methods [a]	4
K nearest neighbors (KNN)	3
Multivariate adaptive regression splines (MARS)	3
Bayesian Network	2
Bagged classification trees	1
Bayesian additive regression trees (BART)	1
Genetic algorithm	1
RF combined with LR	1
RF combined with SVM	1
Fuzzy logic	1
Logistic model tree	1
Naïve Bayes tree	1
Tree-augmented naïve Bayes	1
Alternative traditional statistical methods	5 (7%)
Generalized additive models (GAM)	2
Discriminant analysis	1
Poisson regression	1
Generalized estimating equations (GEE)	1

a This excludes simple bagging and boosting

Table 2. Overview of methods for model validation at study level (n=71). Counts refer to papers. Risk of bias in model validation refers to the first of five bias signaling items that were used in this study.[a] No risk of bias: the item was scored as 'no' for all models in the study; unclear: the item was scored as 'unclear' for at least one model; yes: the item was scored as 'yes' (bias present) for at least one model.

Type of validation	**Validation: risk of bias classification**		**N (%)**
	No	**Unclear/yes**	
None		7	7 (10%)
Single random split	10	19	29 (41%)
Resampling	6	19	25 (35%)
Repeated random splits	3	6	9
Cross-validation	3	12	15
Bootstrapping		1	1
External	7		7 (10%)
Chronological split	4		4
Split by center	1		1
Internal-external CV	1		1
Different dataset	1		1
Type depends on algorithm		3	3 (4%)
Total, n (%)	23 (32%)	48 (68%)	71

[a] Table A.2 describes the five bias items. For bias in model validation, we repeat the description here: We discern two general criteria to assess the validation: first, it should be clear that models are developed using training data only; second, if validation is done using resampling (repeated data splitting, cross-validation, bootstrapping), it should be clear that all model building steps are repeated in every training dataset; ad hoc flaws are documented and tabulated.

Figure 1. PRISMA flowchart

Figure 2. Summary of the five signaling items at study level (n=71). No (green): none of the five items were scored as 'unclear' or 'yes' in the whole study; unclear (orange): at least one item was scored as 'unclear' for at least one model; yes (red): at least one item was scored as 'yes' for at least one model.

Figure 3. Beeswarm plots of AUC difference (AUC of ML method minus AUC of LR) for all 282 comparisons by ML category, overall (panel A) and stratified by risk of bias (panel B). Abbreviations: LR, logistic regression; ML, machine learning; RF, random forest; SVM, support vector machine; ANN, artificial neural network.

Figure 4. Differences in discriminative ability between LR and ML models, overall and according to risk of bias (n=282 comparisons). LR, logistic regression; RF, random forest; SVM, support vector machine; ANN, artificial neural network. When LR was compared with traditional statistical methods (discriminant analysis, Poisson regression, generalized estimating equations, generalized additive models), these methods were not included as 'Other ML methods' and were thus excluded from this plot.

What is new

Key Findings

- Studies comparing clinical prediction models based on logistic regression and machine learning algorithms suffered from poor methodology and reporting, in particular with respect to the validation procedure
- The studies rarely assessed whether risk predictions are reliable (calibration), but the area under the ROC curve (AUC) was almost always provided
- The AUC of logistic regression and machine learning models for clinical risk prediction were similar when fair comparisons were made; ML performance was higher in comparisons that were at high risk of bias

What this adds to what is known

- Machine learning models do not automatically lead to improved performance over traditional methods
- Model validation procedures are often not sound or not well reported, which hampers a fair model comparison in real world case studies

What should change now

- More attention for calibration performance of regression and machine learning models is urgently needed
- Model development and validation methodologies should be more carefully designed and reported to avoid research waste
- Research should focus more on identifying which algorithms have optimal performance for different types of prediction problems

A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models

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CONFLICTS OF INTEREST

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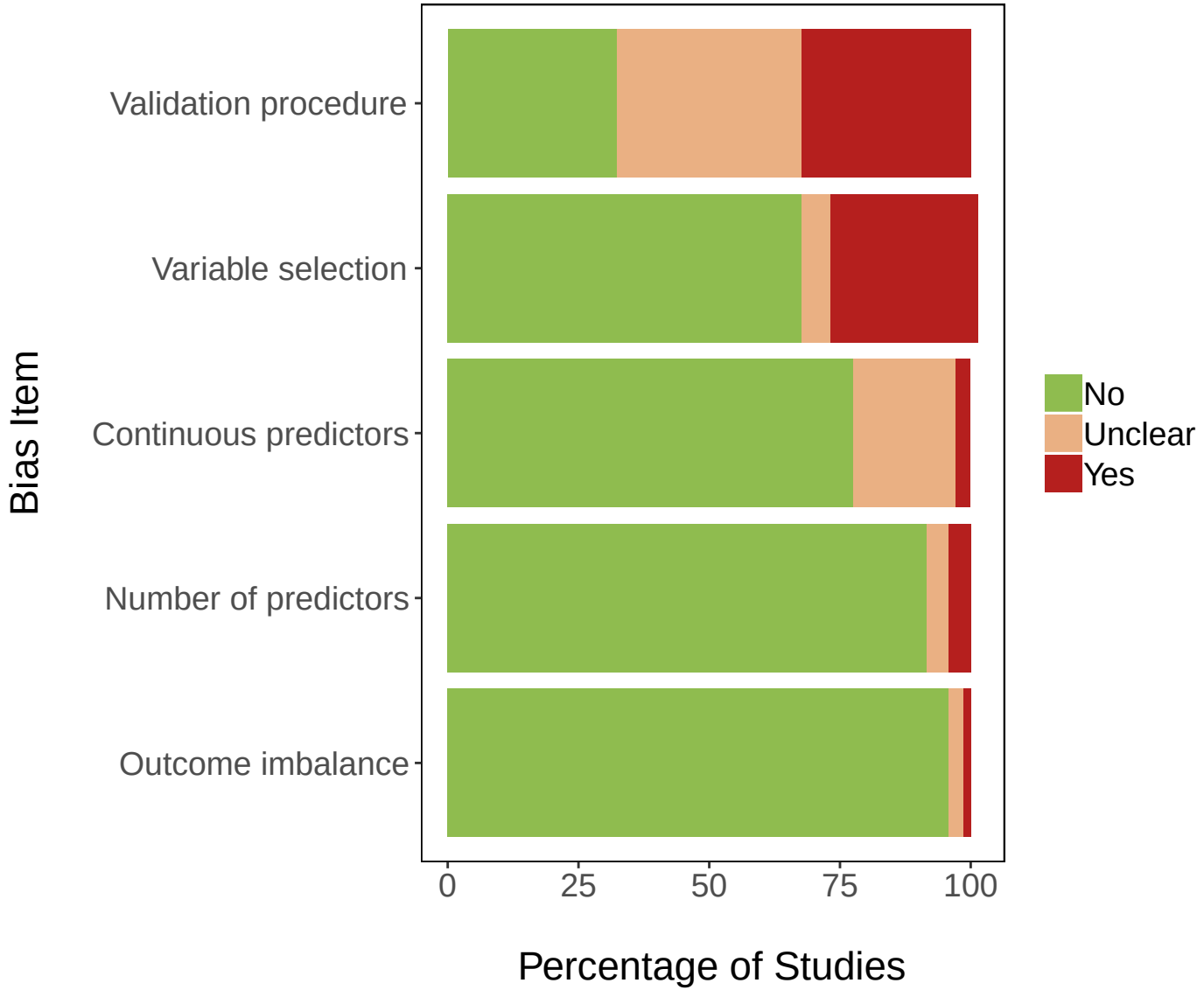
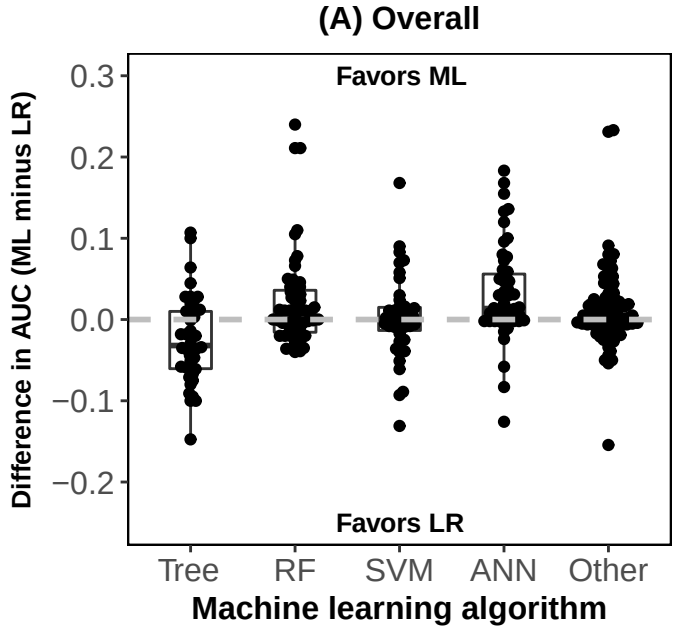
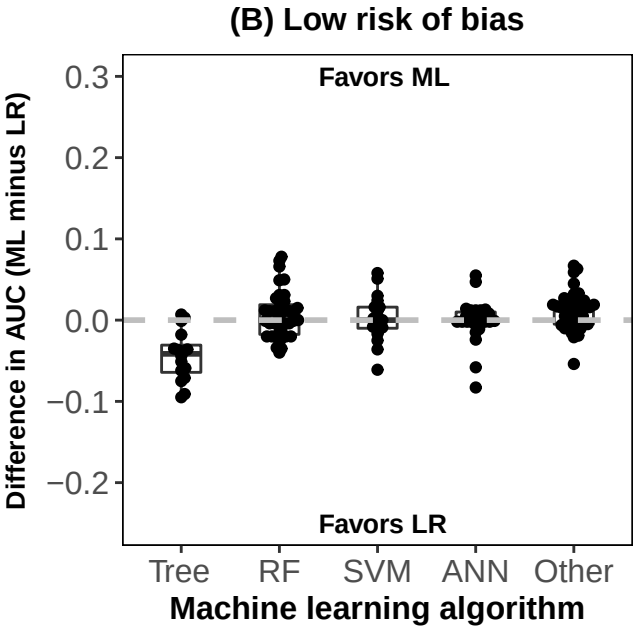
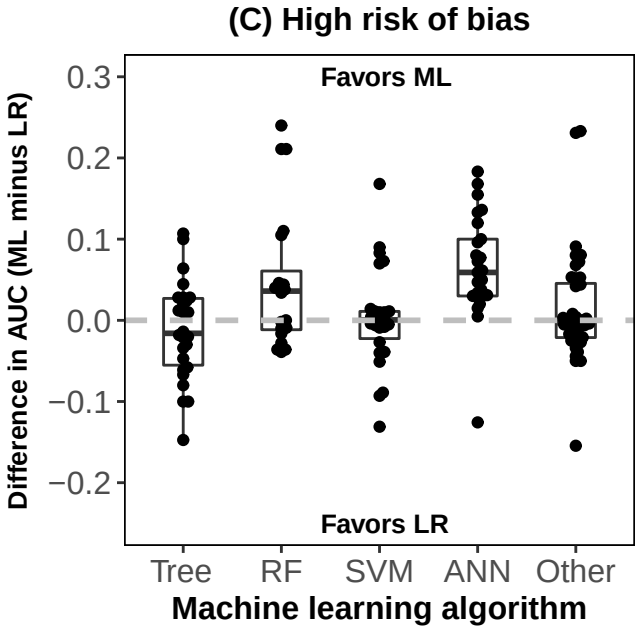
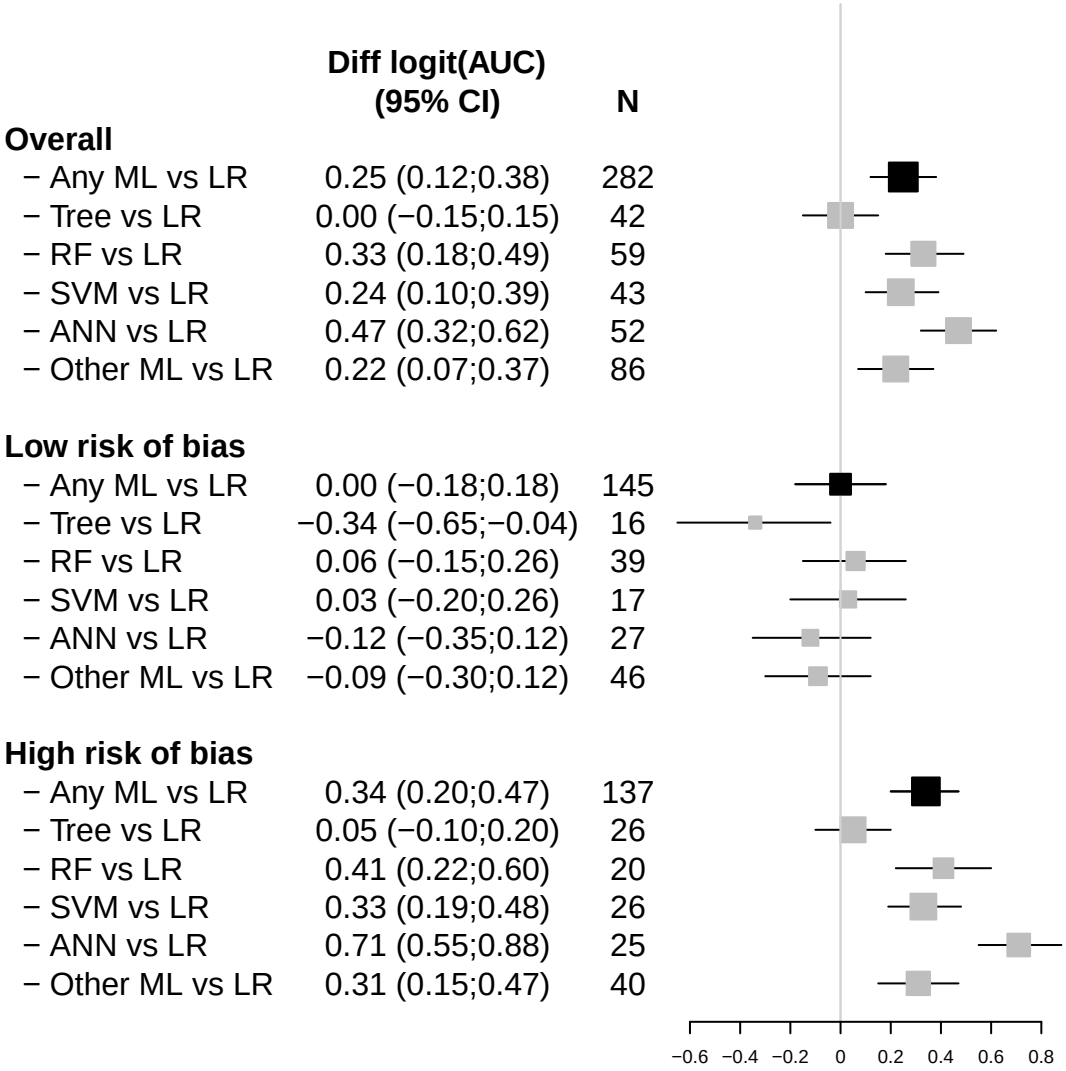
Declaration of interests: none.

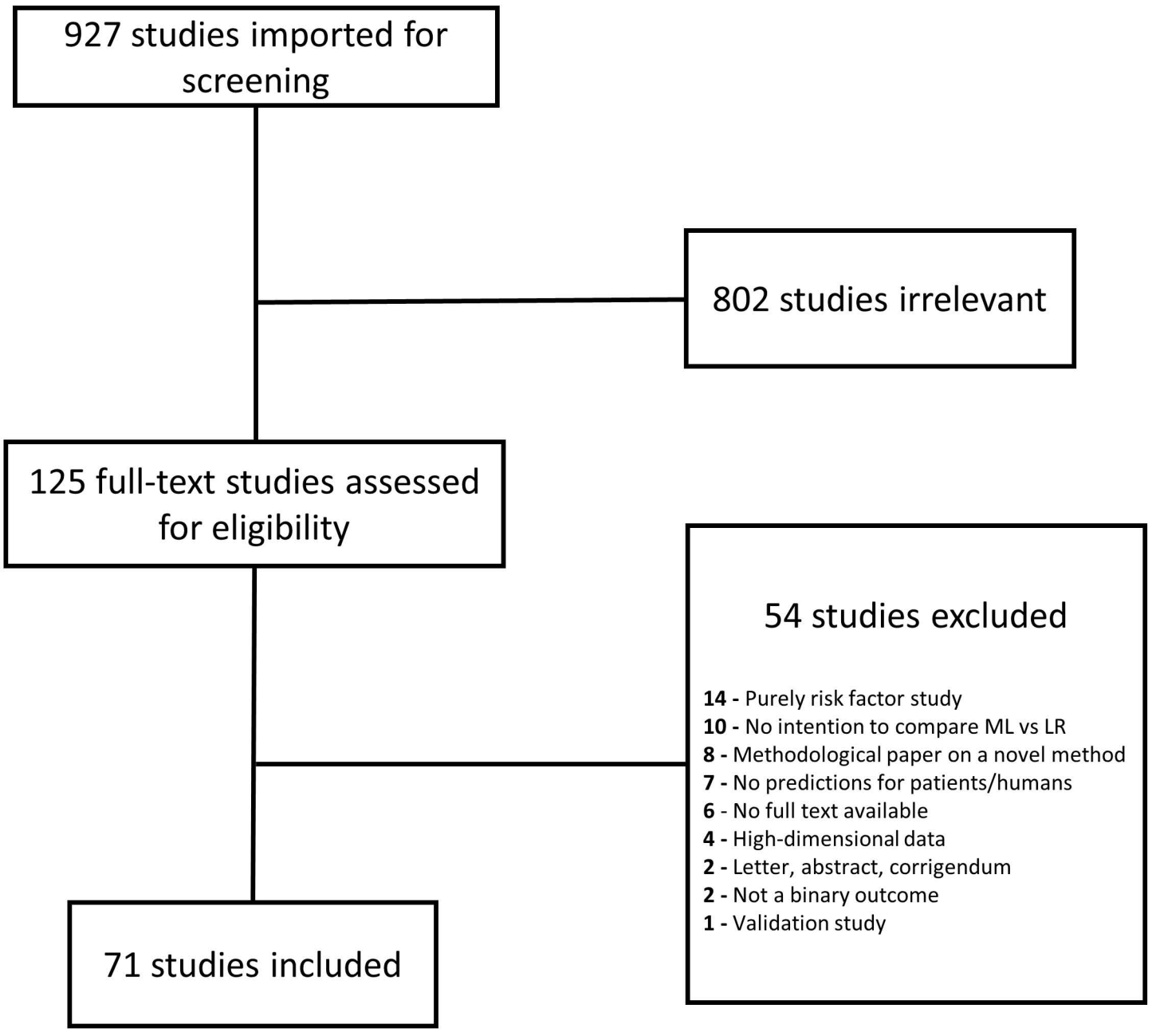

Validation procedure
Variable selection
Continuous predictors
Number of predictors
Outcome imbalance
Bias Item
0
25
50
75
100
Percentage of Studies
No
Unclear
Yes


(A) Overall
Favors ML
Favors LR
Difference in AUC (ML minus LR)
0.3
0.2
0.1
0.0
−0.1
−0.2
Tree
RF
SVM
ANN
Other
Machine learning algorithm


(B) Low risk of bias
Favors ML
Favors LR
Difference in AUC (ML minus LR)
0.3
0.2
0.1
0.0
−0.1
−0.2
Tree
RF
SVM
ANN
Other
Machine learning algorithm


(C) High risk of bias
Favors ML
Favors LR
Difference in AUC (ML minus LR)
0.3
0.2
0.1
0.0
−0.1
−0.2
Tree
RF
SVM
ANN
Other
Machine learning algorithm




927 studies imported for screening
802 studies irrelevant
125 full-text studies assessed for eligibility
54 studies excluded
14 - Purely risk factor study
10 - No intention to compare ML vs LR
8 - Methodological paper on a novel method
7 - No predictions for patients/humans
6 - No full text available
4 - High-dimensional data
2 - Letter, abstract, corrigendum
2 - Not a binary outcome
1 - Validation study
71 studies included

Authors' contributions

E.C. was involved in the conception of the study, data collection, data analysis and interpretation, drafting of the article, and gave her final approval of the version to be published. J.M. was involved in data collection, critical revision of the article, and gave her final approval of the version to be published. G.S.C. was involved in the conception of the study, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. E.W.S. was involved in the conception of the study, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. J.Y.V. was involved in the conception of the study, data collection, interpretation of the data, the critical revision of the article, and gave his final approval of the version to be published. B.V.C. was involved in the conception of the study, data collection, data analysis and interpretation, drafting of the article, and gave his final approval of the version to be published.