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Prediction models for treatment-induced cardiac toxicity in patients with non-small-cell lung cancer: A systematic review and meta-analysis

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ABSTRACT

Background: To maximize the likelihood of positive outcome in non-small-cell lung cancer (NSCLC) survivors, potential benefits of treatment modalities have to be weighed against the possibilities of damage to normal tissues, such as the heart. High-quality data-driven evidence regarding appropriate risk stratification strategies is still scarce. The aim of this review is to summarize and appraise available prediction models for treatment-induced cardiac events in patients with NSCLC.

Methods: A systematic search of MEDLINE was performed using a Boolean combination of appropriate truncation and indexing terms related to "NSCLC", "prediction models", "cardiac toxicity", and "treatment modalities". The following exclusion criteria were applied: sample-size of less than 100, no significant predictors in multivariate analysis, lack of model specifications, and case-mix studies. The generic inverse variance method was used to pool the summary effect estimate for each predictor. The quality of the papers was assessed using the Prediction model Risk Of Bias Assessment Tool.

Results: Of the 3,056 papers retrieved, 28 prediction models were identified, including seven for (chemo-) radiotherapy, one for immunotherapy, and 20 for surgical resection. Forty-one distinct predictors were entered in the prediction models. The pooled effect estimate of the mean heart dose (HR = 1.06, 95%CI:1.04–1.08) and history of cardiovascular diseases (HR = 3.1, 95%CI:1.8–5.36) were shown to significantly increase the risk of developing late cardiac toxicity after (chemo-)radiotherapy. Summary estimates of age (OR = 1.17, 95% CI:1.06–1.29), male gender (OR = 1.61, 95%CI:1.4–1.85), and advanced stage (OR = 1.34, 95%CI:1.06–1.69) were significantly associated with higher risk of acute cardiac events after surgery. Risk of bias varied across studies, but analysis was the most concerning domain where none of the studies were judged to be low risk.

Conclusion: This review highlights the need for a robust prediction model which can inform patients and clinicians about expected treatment-induced heart damage. Identified clues suggest incorporation of detailed cardiac metrics (substructures' volumes and doses).

1. Introduction

Non-Small-Cell Lung Cancer (NSCLC) is the leading cause of cancer-related deaths in both Europe and the USA [1]. Technological advances in cancer therapy have enabled multimodal treatment for NSCLC patients, improving survival. For example, proton therapy delivers a highly localized dose to the target volumes, with better healthy tissue sparing [2]. Minimally invasive resection techniques (e.g. video-assisted thoracoscopic surgery) have improved post-operative fitness [3]. Finally, immunotherapy enables the immune system to control the cancer [4]. All of these therapies have their own efficacy and toxicity profile which are also very patient specific. The possibility to choose among multiple combinations of treatment modalities demands for an accurate quantification of treatment efficacy vs treatment side effects (toxicities) in an individual patient.

Cardiac toxicity is one of the most undesirable treatment-induced side effects for NSCLC patients. It encompasses many cardiological symptoms and adverse events: chest pain, arrhythmias, pericardial

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effusion, myocardial dysfunction, ischemic heart diseases, and lastly heart failure. Short-term toxicities usually have a recovery period within weeks to months, but late events are considered irreversible and they determine cardiac function loss over time [5]. The pathophysiology of cardiac toxicity is characterized by diverse etiological factors: presence of comorbidities prior to treatment, tumor-related variables, and treatment-related parameters [6]. We hypothesize that data-driven risk stratification models that identify patients at high risk of developing cardiac sequalae can be used as decision support tools by clinicians for tailoring treatment strategy.

Machine learning (ML) binds statistical inferring to computer science to automatically learn unknown patterns in data and provide new knowledge on a specific problem [7]. ML augments our brain capacity to process multi-source high dimensional data. Accurate and precise ML models can fulfil their potential to become decision support tools for a better evaluation of treatment side effects and radically change clinical guidelines in NSCLC patients. Finally, quantitative *meta*-analysis of the ML models can be helpful to verify consensus on the most relevant prognostic factors.

Despite numerous studies investigating clinical prediction models for treatment-related cardiac toxicities, previous reviews have focused on either specific treatment modalities [8,9] or exclusively the predictive power of the dosimetric parameters [10]. To the best of our knowledge, this is the first report to provide a broader overview.

The aims of this review are to: 1) summarize available prediction models for cardiac events after different treatment modalities in NSCLC patients, 2) appraise the prediction models from both methodological and clinical perspectives, and 3) discuss possible future directions.

2. Methods

The systematic review and *meta*-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [11].

2.1. Literature search strategy

On February 10, 2021, MEDLINE was searched via PubMed with no language, date, or document type restrictions. The search term was developed using the Boolean combination of the Medical Subject Headings (MeSH) and appropriate truncations associated with the following keywords: “NSCLC”, “prediction models”, “cardiac toxicity”, and “treatment modalities” (full search string provided in Supplementary Material S1).

2.2. Eligibility criteria and study selection

We included original publications:

- That developed a prediction model using any machine learning techniques,
- To predict cardiac toxicities,
- On NSCLC patients that underwent monotherapy or multimodal treatments (i.e. surgery, chemotherapy, radiotherapy, immunotherapy, particle therapy, and/or targeted therapy).

Two independent reviewers (A.T. and F.T.) excluded the irrelevant papers using the following criteria:

- Univariate-only analyses,
- Case-mix studies,
- Lack of model specifications,
- No significant predictors in the multivariate analysis,
- Mixed-outcome models,
- In-vivo/in-vitro studies,
- Conference abstracts or editorials,
- Sample-size of less than 100 patients (to achieve high-quality effect estimates).

Studies were included in *meta*-analysis if the identified predictors were statistically (i.e. type of effect estimates) and clinically (i.e. similar reference group of the categorical variables) homogeneous. The reference lists of the selected articles and the “Similar Articles” section in PubMed were also cross-checked (F.P. and F.T.) to identify further relevant papers.

2.3. Data extraction

One reviewer extracted the following items from the included studies: publication year, sample-size, mean age, gender distribution, country/region, treatment(s), event rate, type of cardiac toxicity (i.e. dependent variable), time-point of outcome assessment, machine learning algorithm, model’s specifications (i.e. intercept, type and size of the effect estimates, and the corresponding 95% Confidence Intervals or CIs), and performance measures. A sample (20%) of the extracted items were double-checked to verify the satisfactory quality of data extraction.

2.4. Quantitative data synthesis

The summary effect estimate for each predictor was calculated (Odds Ratio (OR) for logistic regression and Hazard Ratio (HR) for cox proportional hazard models). The generic inverse variance method was used to obtain the summary effects and statistical weight of the studies [12]. To determine the statistical heterogeneity between the studies for each predictor, the $\chi 2$ of the Cochran’s Q-test and the I^2 statistic were calculated [13]. Based on the level of heterogeneity, the random- or fixes-effect models was used. If the level of heterogeneity was not significant ($P > 0.05$ in Q-test or I^2 less than 50%), a fixed-effect model was employed to estimate the summary effect. Otherwise, a random-effect model was used. Quantitative syntheses were performed using the Review Manager software (RevMan v.5.4, The Cochrane Collaboration, 2020).

2.5. Risk of bias assessment

The Prediction model Risk Of Bias Assessment Tool (PROBAST) was used to perform quality assessment of the included studies [14]. PROBAST was specifically designed to assess the risk of bias of the studies which include either development or validation of a prediction model. PROBAST has four domains: participants, predictors, outcome, and analysis with a total of 20 signaling questions. Each signaling question was answered on the 5-point scale as no, probably no, yes, probably yes, or no information. Each domain was judged as low, high, or unclear risk of bias based on the answers to the signaling questions.

3. Results

3.1. Study selection

The database search returned 3,056 studies. Of these, 2,929 were excluded during title and abstract screening because they did not meet inclusion criteria. Full-text review of the remaining 127 articles resulted in inclusion of 28 papers in qualitative synthesis. Furthermore, 18 studies were used to calculate the summary effect estimates of the predictors. Manual searches did not identify any relevant publications. The details of the study selection process are shown in Fig. 1.

3.2. Characteristics of the included studies

The key characteristics of the included studies are listed in Table 1. Of the 28 included papers, seven studies developed prediction models

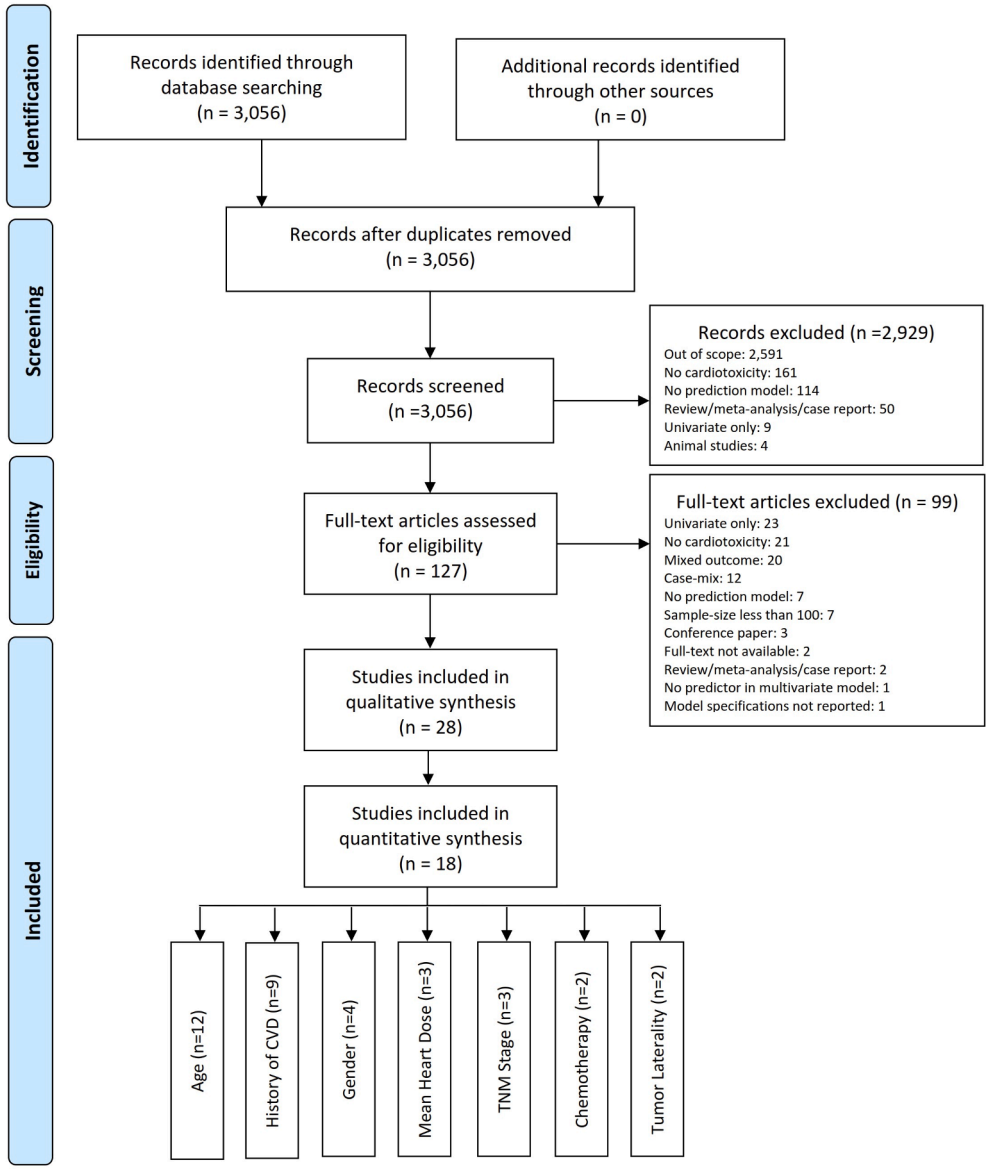


Fig. 1. PRISMA flow diagram of the study selection process (see abbreviations in Table 1).

for late cardiac toxicity after (chemo-)radiotherapy [15–21]. We identified 20 prediction models for acute cardiac events after surgery [22–41] and one study estimated the risk of developing cardiovascular events after immunotherapy (nivolumab and pembrolizumab) [42].

The studies were published between 1993 and 2020 and approximately 42.9% of the studies were performed in the United States. The remaining studies were performed in Japan, Italy, China, United Kingdom, Canada, and Switzerland. The median sample size of studies was 288 and the median male gender distribution was 56.6%. Furthermore, three studies included elderly patients [15,26,42].

Twelve studies (42.9%) included patients who underwent surgical resection as the sole treatment method [22,26–30,33,35–37,39,40] and eight studies (28.6%) assessed cardiac events after combined therapy of surgery with chemotherapy and/or radiotherapy [23–25,31,32,34,38,41]. Five studies (17.9%) considered radiotherapy (3D-conformal radiotherapy, intensity-modulated radiotherapy, or radioactive implant) with or without chemotherapy as the eligibility criteria of their study samples [15,17–20]. Moreover, two studies (7.1%) included the patients in clinical trials who received either photon (intensity-modulated) or proton beam therapy [16,21].

3.3. Cardiac toxicity

The cardiac event rate in the study samples ranged between 3.9% and 49.6%. Atrial fibrillation, arrhythmia, pericardial effusion, and ischemic heart diseases were considered as the primary end point in 12 (42.9%) [27,28,30–32,34–40], 4 (14.3%) [22–24,29], 2 (7.1%) [16,21], and 1 (3.6%) studies [15], respectively. Nine studies (32.1%) used all types of cardiac events as the outcome. Nineteen studies (67.9%) measured acute cardiac side effects after surgical resection and the remaining nine studies recorded late cardiac toxicities occurring at least three months after treatment completion. Electrocardiography (n = 16, 57.1%) [22,24,26–36,38–40], Common Terminology Criteria for Adverse Events (CTCAE) (n = 3, 10.7%) [17,19,21], and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (n = 2, 7.1%) [15,42] were the most frequently used instruments for assessing or grading the cardiac events.

3.4. Analysis of the risk factors for cardiac toxicity

The most frequent risk factors for the treatment-induced cardiac toxicity were: Age (n = 14), history of cardiovascular diseases (n = 13),

Table 1
Characteristics of the prediction model development studies for treatment-induced cardiac toxicity in non-small-cell lung cancer patients.

Study	Year	Country	Sample Size	Male	TNM Stage	Acute/ Late	Outcome	Coefficient	Prediction Equation	Performance Measures
Prediction Models for Cardiotoxicity after **(Chemo-)Radiotherapy**										
Hardy et al. [15]	2010	USA	34,209	18,875	Every stage	Late	IHD	HR	(1.25 × Age between 80 and 84)+(1.45 × Age ≥ 85)+(0.83 × Female)+(1.24 × CT-only)+(0.85 × RT-only)+(1.32 × Comorbidity Score = 2)+(1.56 × Comorbidity Score = 3)+(0.77 × Comorbidity Score ≥ 4)+(1.15 × Stage IIIB)+(1.31 × Stage IIIA)+(1.4 × Stage II)+(1.34 × Stage I)+(1.38 × Unstaged)*	–
Ning et al. [16]	2017	China	201	113	Every stage	Late	PE	HR	(2.14 × HV35)+(0.52 × Tumour Location Right vs. Left)+(2.82 × Adjuvant CT)+(1.68 × Cardiac History)*	–
Dess et al. [17]	2017	USA	125	95	II-III	Late	CE	HR	(2.96 × Pre-existing Cardiac Disease)+(1.07 × Mean Heart Dose)*	–
Yegya-Raman et al. [18]	2018	USA	140	77	II-III-IV	Late	CE	HR	(3.54 × CAD)+(1.065 × Mean Heart Dose)*	–
Chen et al. [19]	2019	China	137	84	III	Late	CE	HR	(2.225 × Age)+(2.852 × Pre-CAD)+(3.727 × HV30)+(3.584 × GLS at Baseline)*	–
Atkins et al. [20]	2019	USA	748	380	II-III	Late	CE	HR	(1.01 × Age)+(7 × CHD)+(1.55 × Arrhythmia)+(0.39 × IMRT)+(1.05 × Mean Heart Dose)+(0.95 × Cardiac Dose × CHD) *	–
Niedzielski et al. [21]	2020	USA	141	77	III	Late	PE	B	−1.37+(-0.009 × Age)+(0.021 × Female)+(-0.038 × Right Upper Lobe Tumour)+(-0.156 × CVD)+(0.026 × WH Mean Dose)+(0.931 × WH V55)+(2.013 × WH V60)+(0.823 × WH V65)+(2.016 × WH V70)+(0.007 × LA Volume)+(0.008 × LA Mean Dose)+(0.473 × LA V5)+(0.134 × LA V20)+(0.342 × LA V25)+(0.288 × LA V30)+(0.089 × LA V35)+(0.072 × LA V55)+(0.373 × LA V60)+(0.043 × LA V65)+(0.012 × RV Max Dose)	AUC = 0.82 Calibration Slope = 1.356
Prediction Model for Cardiotoxicity after **Immunotherapy**										
Bishnoi et al. [42]	2020	USA	6405	3383	IV	Late	CVD	HR	(1.04 × Age between 70 and 74)+(1.11 × Age between 75 and 79)+(1.24 × Age ≥ 80)+(0.86 × Female)+(0.81 × Immunotherapy) +(1.15 × CCI = 1)+(1.32 × CCI = 2)+(1.56 × CCI ≥ 3)+(0.85 × Adenocarcinoma)+(1.23 × Obesity)+(1.25 × Smoking) +(1.92 × Pre-existing CVD)+(0.91 × Radiotherapy)*	–
Prediction Models for Cardiotoxicity after **Surgery**										
Asamura et al. [22]	1993	Japan	267	190	NA	Acute	CA	B	−8.25+(0.09 × Age)+(0.53 × Extent of Pulmonary Resection)	–
Amar et al. [23]	1995	USA	116	56	NA	Acute	CA	RR	(3.5 × Intraoperative Blood Loss ≥ 1 L)+(3.6 × Tricuspid Regurgitation Jet ≥ 2.7 m/s)*	–
Sekine et al. [24]	2001	USA	244	153	Every stage	Acute	CA	OR	(2.93 × Major Resection)+(4.67 × COPD)*	–
Licker et al. [25]	2002	Switzerland	193	145	Every stage	Acute	CE	OR	−1.99+(3.7 × Age ≥ 70)+(1.4 × Stage III-IV)	–
Brunelli et al. [26]	2004	Italy	109	NA	NA	Acute	CE	B	(1.11 × Concomitant Cardiac Disease)+(-0.18 × Low Height Climbed at Preoperative Stair Climbing Test)*	–
Neragi et al. [27]	2008	USA	127	94	NA	Acute	AF	OR	(2.8 × Age > 65)+(1.3 × Male)+(7.2 × EPP)+(0.8 × Heart Rate > 72 bpm)+(0.9 × Left-Lung Affected)+(0.4 × CAD History)*	H-L P = 0.9

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Country	Sample Size	Male	TNM Stage	Acute/ Late	Outcome	Coefficient	Prediction Equation	Performance Measures
Nojiri et al. [28]	2010	Japan	126	84	Every stage	Acute	AF	RR	(1.81 × Ratio of Early Trans-mitral Velocity/Tissue Doppler Mitral Annular Early Diastolic Velocity)*	AUC = 0.83
Onaitis et al. [29]	2010	USA	13,906	6870	Every stage	Acute	CA	OR	(1.79 × Age)+(1.57 × Male)+(0.67 × Black Race)+(1.24 × Stage II and above)+(1.95 × Pneumonectomy vs. Lobectomy)+(1.69 × Bi-lobectomy vs. Lobectomy) *	–
Hollings et al. [30]	2010	USA	360	153	NA	Acute	AF	OR	(0.922 × Age)+(16.957 × Pre-existing AF or Arrhythmia)*	–
Imperatori et al. [31]	2012	Italy	454	369	Every stage	Acute	AF	OR	(5.91 × Paroxymal AF)+(3.61 × Peri-operative Blood Transfusion)+(3.39 × Post-operative FBS)*	AUC = 0.75H-L P = 0.433
Anile et al. [32]	2012	Italy	134	102	III	Acute	AF	B	(0.731 × LA Area)*	–
Wotton et al. [33]	2013	UK	703	401	II-III-IV	Acute	CE	OR	−3.03+(0.75 × ThRCRI between 1 and 1.5)+(2.94 × ThRCRI between 2 and 2.5)+(4.12 × ThRCRI > 2.5)	AUC = 0.57 R^2 = 0.007
Ivanovic et al. [34]	2014	Canada	363	168	Every stage	Acute	AF	OR	(2.3 × Age ≥ 70)+(4 × Angioplasty/ Stents/Angina)+(3.7 × Thoracotomy)+(16.5 × Converted Surgery)+(7.1 × Stage IV)*	AUC = 0.81H-L P = 0.89
Xin et al. [35]	2014	Japan	186	118	NA	Acute	AF	OR	(0.9 × Side of Lobectomy)*	–
Ai et al. [36]	2015	USA	703	377	NA	Acute	AF	OR	(1.036 × Age)+(1.723 × Male)+(3.708 × CCB Use)*	–
Iwata et al. [37]	2016	Japan	377	262	NA	Acute	AF	OR	(5.32 × Male)+(3.92 × Resected Segments)+(2.67 × BNP)*	–
Muranishi et al. [38]	2017	Japan	593	350	Every stage	Acute	AF	OR	(1.09 × Propensity Score)+(3.06 × Lymph Node Dissection)*	–
Garner et al. [39]	2017	UK	376	167	NA	Acute	AF	B	(0.07 × Age)+(1.482 × Post-operative Infection)*	–
Ueda et al. [40]	2018	Japan	607	294	I	Acute	AF	OR	(1.059 × Age)+(5.734 × Lobectomy vs. Segmentectomy)+(2.182 × FEV1 less than 70%)*	–
Osawa et al. [41]	2020	Japan	309	188	I-II-III	Late	CE	HR	(4.93 × Advanced Stages of Lung Cancer)+(1.95 × CAC Score)*	–

Abbreviations (alphabetic order): AF, Atrial Fibrillation; AUC, Area Under the Curve; BNP, Brain Natriuretic Peptide; CA, Cardiac Arrhythmia; CAC, Coronary Artery Calcium; CAD, Coronary Artery Disease; CCB, Calcium Channel Blockers; CCI, Charlson Comorbidity Index; CE, Cardiac Events; CHD, Coronary Heart Disease; COPD, Chronic Obstructive Pulmonary Disease; CT, Chemotherapy; CVD, Cardiovascular Diseases; EPP, Extrapleural Pneumonectomy; FBS, Fibrobronchoscopy; FEV, Forced Expiratory Volume; GLS, Global Longitudinal Strain; H-L P, Hosmer-Lemeshow P-value; HR, Hazard Ratio; HV, Heart Volume; IHD, Ischemic Heart Diseases; IMRT, Intensity-Modulated Radiation Therapy; LA, Left Atrium; NA, Not Available; OR, Odds Ratio; PE, Pericardial Effusion; RR, Relative Risk; RT, Radiotherapy; RV, Right Ventricle; ThRCRI, Thoracic Revised Cardiac Risk Index; TNM, Tumor-Lymph node-Metastasis; UK, United Kingdom; USA, United States of America; VATS, Video-Assisted Thoracic Surgery; WH, Whole Heart.
*The intercept of the multivariate model was not reported.

atrial volume parameters (n = 10), gender (n = 7), type of resection technique (n = 7), heart volume measures (n = 6), Tumor-Node-Metastasis (TNM) stage (n = 5), mean heart dose (n = 4), laterality of tumor location (n = 4), radiotherapy (n = 3), chemotherapy (n = 2), and Charlson comorbidity index (n = 2). Fig. 2 presents the frequency of times that each variable was either considered as a candidate predictor or entered in the final prediction model.

The forest plot of the pooled hazard ratios of the identified risk factors for late cardiac toxicity after (chemo-)radiation is shown in Fig. 3. Mean heart dose (HR = 1.06, 95% CI:1.04 to 1.08) and history of cardiovascular diseases (HR = 3.1, 95% CI:1.8 to 5.36) were shown to significantly increase the risk of developing cardiac toxicity. In contrast, the summary effect estimates for age (HR = 1.38, 95% CI:0.95 to 1.99) and chemotherapy (HR = 1.8, 95% CI:0.81 to 4.02) were not statistically significant.

As shown in Fig. 4, summary estimates of age (OR = 1.17, 95% CI:1.06 to 1.29), male gender (OR = 1.61, 95% CI:1.4 to 1.85), and advanced TNM stage (OR = 1.34, 95% CI:1.06 to 1.69) were significantly associated with higher risk of acute cardiac events after surgical resection. However, no significant predictive value was shown for history of cardiovascular diseases (OR = 3.6, 95% CI:0.93 to 13.97) and left laterality (OR = 0.9, 95% CI:0.81 to 1).

3.5. Quality assessment

Fig. 5 shows the grading of PROBAST signaling questions and the summary risk of bias for the participants, predictors, outcome, and analysis domains. Less than half of the studies were either at low or unclear risk of bias for the participants and predictors domains, but all studies were at high risk of bias in the analysis domain. All included studies used regression analysis as the machine learning algorithm. Four studies documented the reason for method selection [21,33,37,38] and only one study performed systematic review as the predictor selection technique before modeling [37].

Implicit or explicit predictor importance assessment was performed in five studies mostly focusing on cardiac parameters (e.g. coronary artery calcium score, whole heart volume, or dose-volume metrics from the substructures of the heart) [16,18,21,27,41].

The interaction terms were assessed in two studies (i.e. mean heart dose × pre-existing coronary heart disease [20] and chemotherapy-only × radiotherapy-only × chemoradiotherapy treatments [15]). Moreover, one study used elastic net regression as the penalized regression method [21].

Twenty-four studies (85.7%) did not report the intercept of the prediction models. Only five studies (17.9%) assessed the discrimination power in terms of the area under the receiver operating characteristic curve [21,28,31,33,34]. Furthermore, the Hosmer-Lemeshow test or

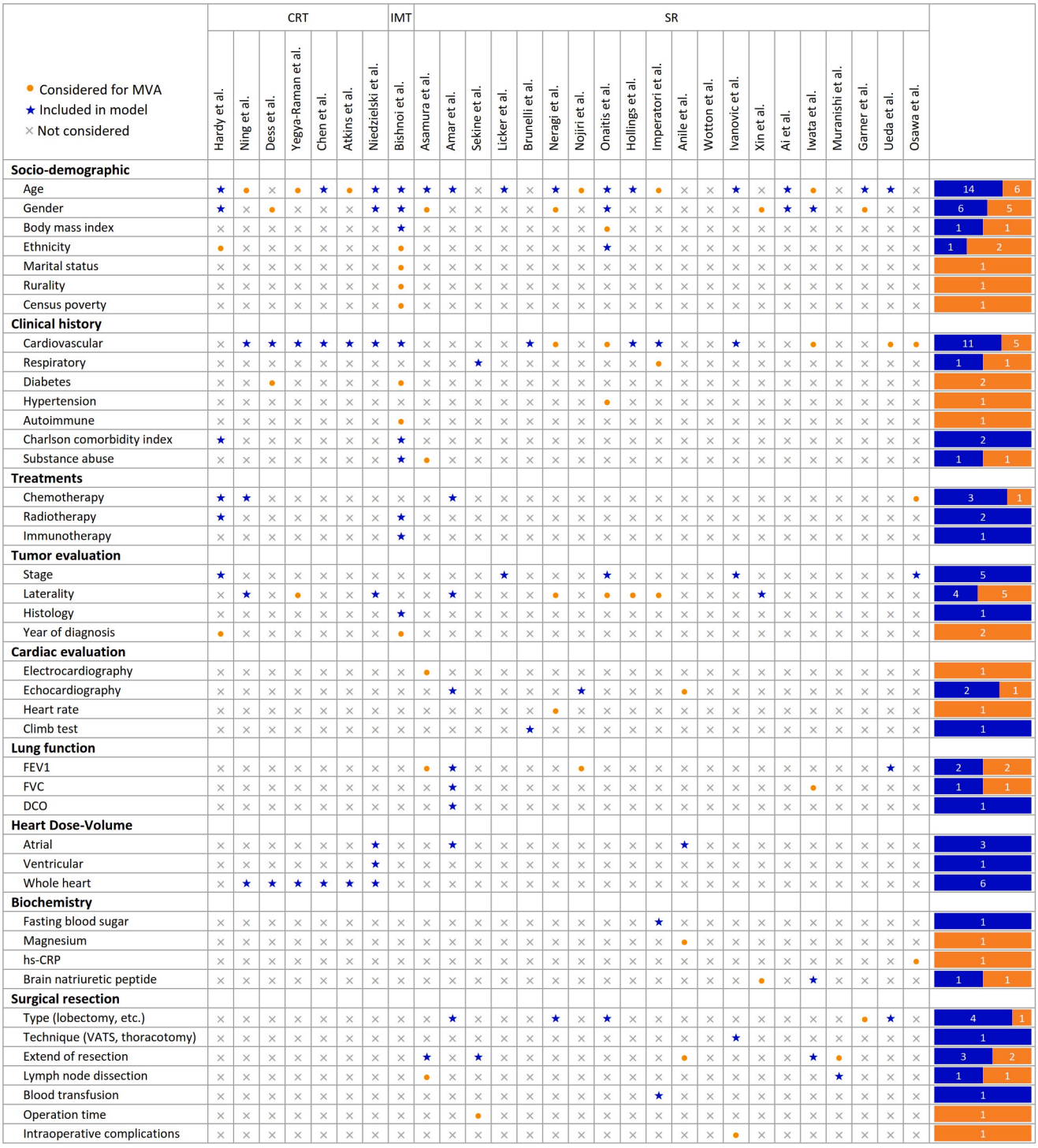


Fig. 2. Most common predictors considered and included. Considered: the predictor was used as a candidate predictor in multivariable analysis. Included: the predictor was entered in the final prediction model (Abbreviations: CRT, (Chemo-)Radiotherapy; DCO, Diffusing capacity of the lungs for carbon monoxide; FEV1, Forced Expiratory Volume1; FVC, Forced Vital Capacity; hs-CRP, high-sensitivity C-Reactive Protein; IMT, Immunotherapy; VATS, Video-Assisted Thoracoscopic Surgery; MVA, Multivariate Analysis; SR, Surgical Resection).

calibration slope were used in four studies (14.3%) to estimate the agreement between the predicted probabilities and observed outcomes [21,27,31,34].

4. Discussion

Cardiac toxicity is a complex multifactorial treatment-induced side-effect in patients with NSCLC. Quantification of the risk of cardiac toxicity can support the optimization of the treatment strategy for these patients. This systematic review identified 20 prediction models for acute surgical-related cardiac events as well as seven risk models for late cardiac toxicity after radiotherapy with or without chemotherapy. One study developed a prediction model to predict cardiovascular diseases after immunotherapy. However, there were not enough performance

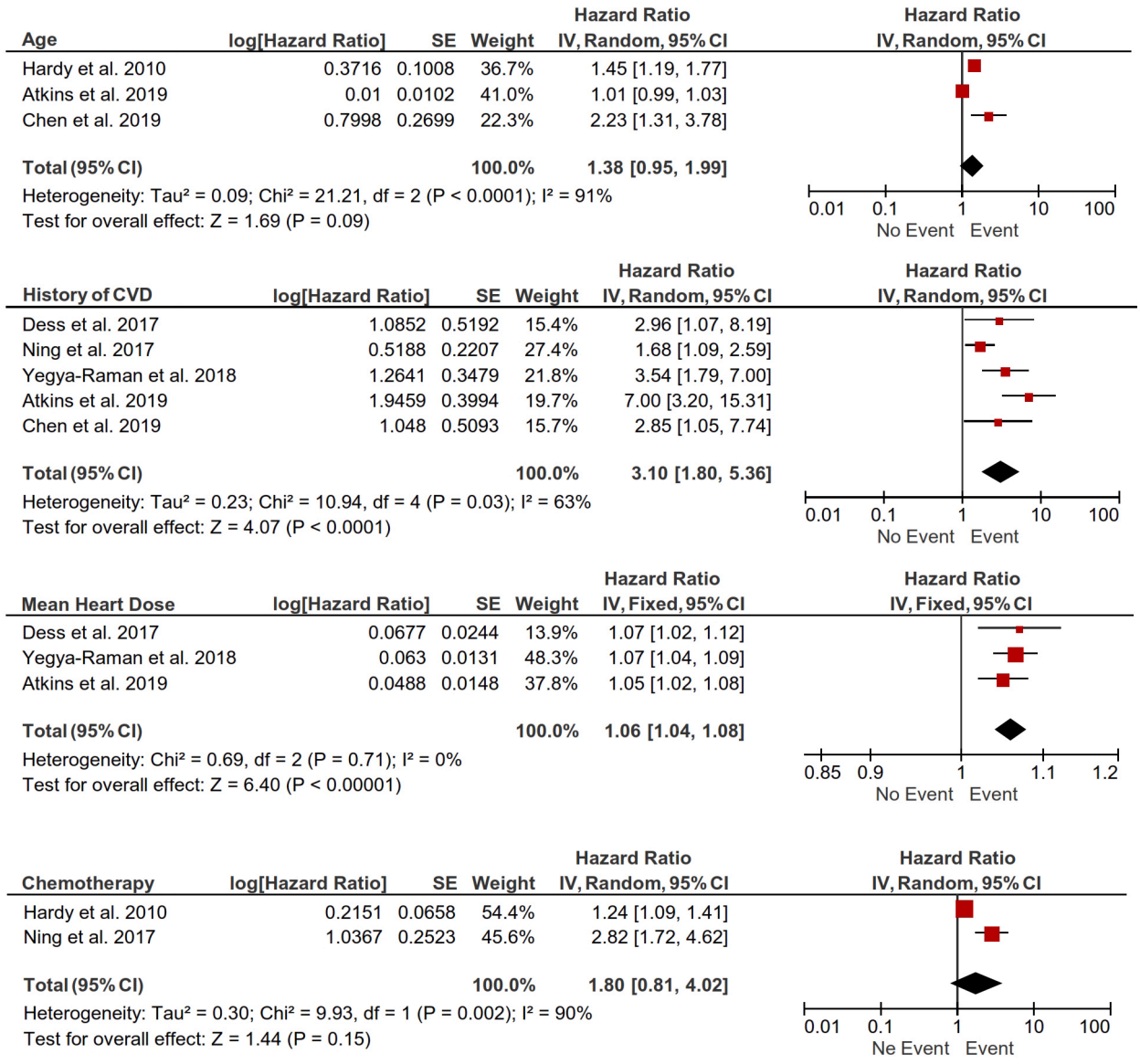


Fig. 3. Pooled effect estimates and their corresponding 95% CIs for risk factors of late cardiac toxicity (age, history of cardiovascular diseases, mean heart dose, and chemotherapy) after (chemo-)radiotherapy in non-small-cell lung cancer patients.

measures reported to enable the applicability of any of these models in clinical practice.

On *meta*-analysis, cardiac radiation dose was significantly associated with a higher risk to develop late cardiac toxicity after (chemo-)radiotherapy with a hazard of 1.06 per Gy increase in mean heart dose. Several large retrospective and prospective series have shown a similar dose–response relationship with cardiac events [43]. Previous studies found that higher ventricular doses were associated with cardiac disease biomarkers (e.g. troponin levels and brain natriuretic peptide) [44]. Furthermore, another study found that mean heart dose may underestimate the doses to the cardiac substructures and for optimal heart sparing investigations, the authors recommended to consider cardiac substructures as separate organs at risk [45]. Independently of the cardiac dose, a history of cardiovascular comorbidities was also significantly associated with a nearly three-fold increase in the likelihood of developing cardiac toxicity, which is in line with the previously published studies [46]. Although conflicting evidence is available about the effect of age and chemotherapy, summary effect estimates showed no significant associations.

The quantitative synthesis of the risk factors for acute cardiac events after surgery showed that while age, male gender, and advanced TNM stage had significant relationship with the outcome, the odds ratio of history of cardiovascular diseases and left tumor laterality were not statistically significant. Previous publications confirm the predictive value of age and male gender in non-cardiac thoracic surgery [47]. It should be noted that contradictory results are available about the association of previous cardiovascular diseases and tumor laterality. Therefore, further studies are required to clarify their predictive values.

The result of this review showed that poor quality of the models is a remarkable issue. We identified the following areas of concerns. Lack of reporting model's intercept prevents future investigators to perform external validation studies. This limitation hampers the broader clinical application of the prediction models. In confirmation, in different clinical settings, while the number of publications developing prediction models has been widely increasing in the recent years, very few models are actually used in clinical practice [48]. Using the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) checklist can improve the quality of the prediction model papers which in turn paves the way for further evaluation studies [49]. Practical guidelines are available which can help

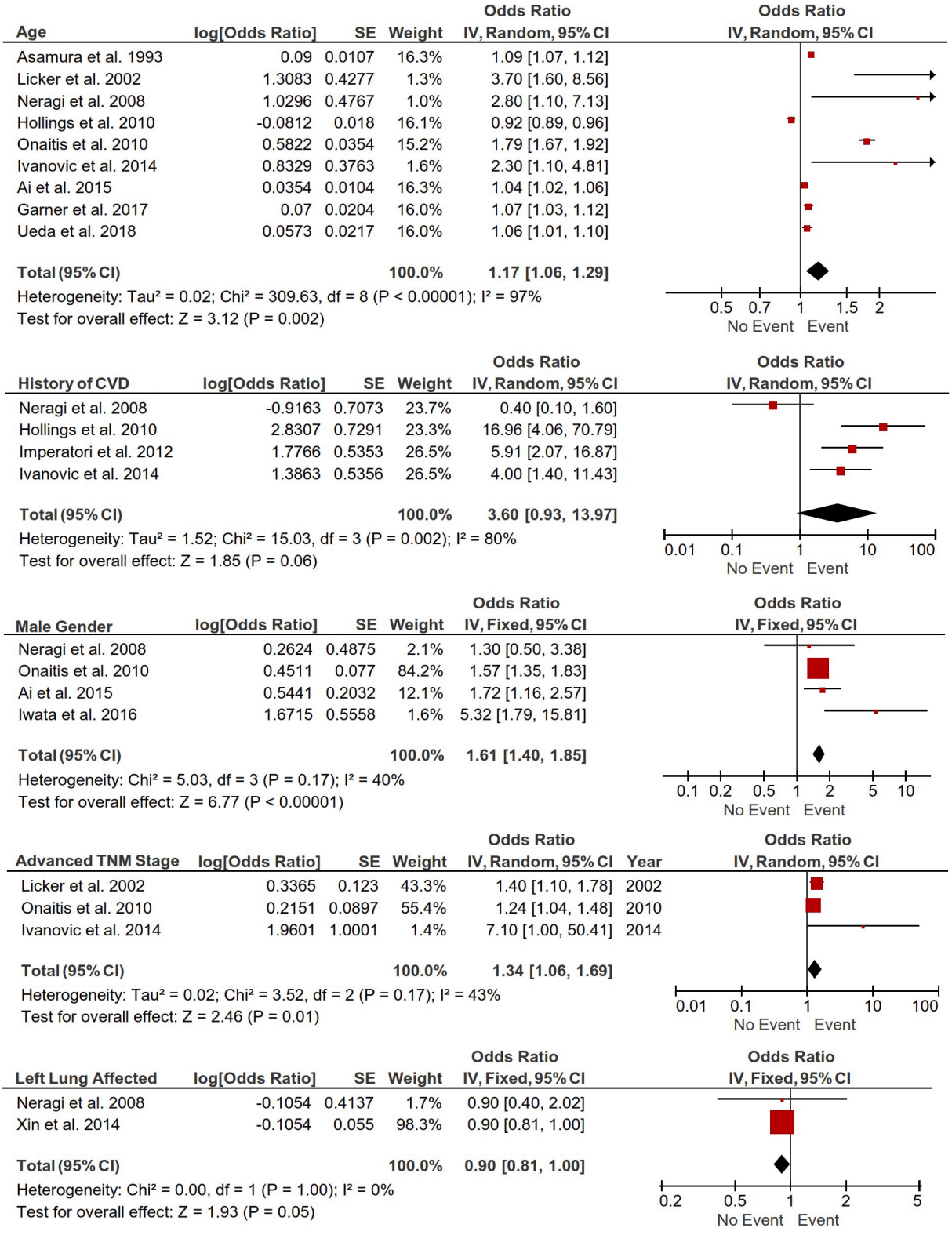
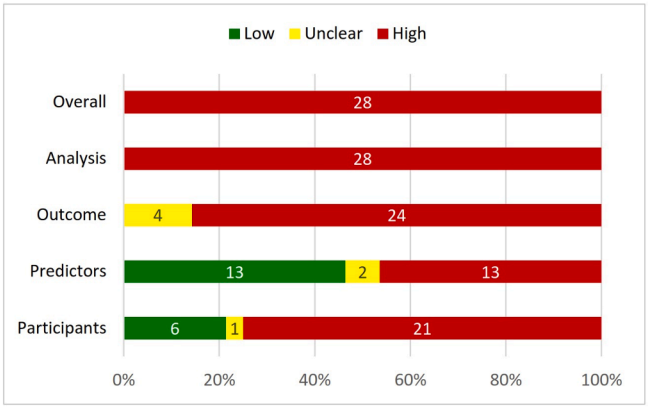


Fig. 4. Pooled effect estimates and their corresponding 95% CIs for risk factors of acute cardiac toxicity (age, history of cardiovascular diseases, gender, TNM stage, and laterality of tumor location) after surgery in non-small-cell lung cancer patients.

researchers in performing and transparent reporting of the diagnostic or prognostic models in developing, validating, or updating studies [50].

All the reviewed papers used regression analysis as the modeling technique. Although, these models are considered as the most interpretable machine learning solution, they are not the optimal technique to detect complex relationships between the variables. A wide variety of machine learning algorithms are available which can be used based on the number of unique data points and type of the dependent variable. For example, decision trees and Bayesian networks are robust classical techniques which can segment data sets into regions according to fixed



	Study	Participants		Predictors			Outcome						Analysis								
		Q1	Q2	Q1	Q2	Q3	Q1	Q2	Q3	Q4	Q5	Q6	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
CRT	Hardy et al.	−	−	+	?	+	+	+	+	+	?	+	+	−	?	?	+	+	−	−	+
	Ning et al.	+	+	+	+	+	−	−	+	+	−	+	+	−	?	?	−	+	−	−	+
	Dess et al.	+	−	+	+	−	+	+	−	+	+	+	−	+	?	?	−	−	−	−	+
	Yegya-Raman et al.	−	−	+	+	+	+	+	−	+	−	+	+	+	?	?	−	+	−	−	+
	Chen et al.	+	+	+	+	−	+	+	−	−	+	−	−	+	?	?	−	−	−	−	+
	Atkins et al.	−	+	+	+	+	+	−	−	−	?	+	−	+	?	?	−	+	−	−	+
	Niedzielski et al.	+	+	+	+	+	+	+	−	−	?	+	−	+	?	?	+	−	+	+	+
IMT	Bishnoi et al.	−	+	+	+	+	+	+	−	−	?	+	?	−	?	?	+	−	−	−	+
SR	Asamura et al.	−	?	−	?	−	+	−	−	−	?	+	+	+	?	?	−	−	−	−	+
	Amar et al.	+	+	+	+	−	+	−	+	+	?	+	−	−	−	−	−	−	−	−	+
	Sekine et al.	−	−	+	+	+	+	−	+	+	?	+	+	−	−	−	−	−	−	−	+
	Licker et al.	−	−	−	+	+	+	−	+	+	?	+	+	−	?	?	−	−	−	−	+
	Brunelli et al.	+	+	+	+	−	+	+	−	+	?	+	−	+	?	?	−	−	−	−	+
	Neragi et al.	−	+	+	?	+	+	+	−	+	?	+	−	−	?	−	−	−	−	−	+
	Nojiri et al.	+	−	?	+	−	+	+	+	+	?	−	+	+	?	?	−	−	+	−	+
	Onaitis et al.	−	+	+	+	+	+	+	−	+	?	+	+	+	−	+	−	−	−	−	+
	Hollings et al.	−	−	+	+	+	+	+	−	+	?	+	+	+	?	?	−	−	−	−	+
	Imperatori et al.	−	−	+	+	+	+	+	−	−	?	+	−	+	−	?	−	−	+	−	+
	Anile et al.	+	+	+	+	−	+	+	+	+	?	−	+	+	+	?	−	−	−	−	+
	Wotton et al.	+	?	+	+	−	+	+	−	+	?	+	−	−	?	?	+	−	+	−	+
	Ivanovic et al.	−	−	+	+	+	+	+	−	+	?	+	−	−	−	?	−	−	+	−	+
	Xin et al.	−	−	+	+	−	+	+	+	−	?	+	+	+	+	−	−	−	−	−	+
	Ai et al.	−	+	+	+	+	+	+	+	+	?	+	+	+	+	?	+	−	−	−	+
	Iwata et al.	−	+	+	+	−	+	?	−	+	?	+	−	+	+	?	−	−	−	−	+
	Muranishi et al.	−	+	+	+	−	+	+	+	+	?	−	−	+	−	?	−	−	−	−	+
	Garner et al.	−	+	+	+	+	+	+	+	+	?	+	+	+	+	?	−	−	−	−	+
	Ueda et al.	−	−	+	+	+	+	+	+	+	?	+	−	−	+	−	−	−	−	−	+
	Osawa et al.	−	+	+	+	−	+	+	−	+	?	−	−	+	+	?	−	−	−	−	+

Fig. 5. Answers to signaling questions from the Prediction model Risk Of Bias Assessment Tool (PROBAST) and the overall assessment of four domains: participants, predictors, outcome, and analysis.

rules. As the size of the dataset increases, more advanced deep learning algorithms may be more suitable to predict the outcome [51]. Due to the plethora of possible contributing factors and ML algorithms, there is not a specific solution for predicting cardiac toxicity. A typical workflow of developing a prediction model for cardiac toxicity is suggested in Fig. 6.

Several limitations should be declared for this review. First, due to lack of unique definition for cardiac toxicity, studies considering all types of cardiac events as the primary outcome were included. Second, six out of nine summary effects were derived using random-effect models due to inevitably heterogeneous research designs. Third, in order to include homogenous effect estimates, studies with univariate analyses were not included. However, more predictors with weaker level of association could have been identified in those papers. Fourth, the majority of the models were trained with limited data sets and with regression classifiers which are not optimal machine learning algorithms for discovering non-linear associations. Fifth, poor quality of the

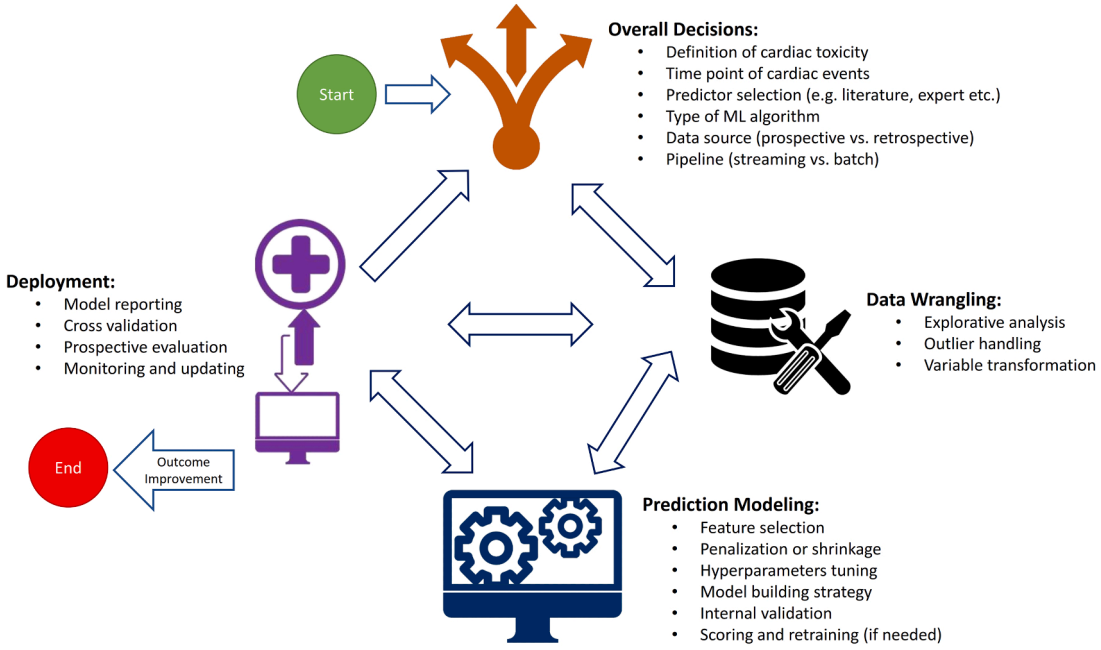


Fig. 6. Typical lifecycle of Machine Learning (ML)-based prediction models for cardiac toxicity.

included studies limits the clinical value of pooled effect estimates. On the other hand one of the main strengths of the study was that, the majority of the papers that reported a prediction model for (chemo-) radiation were recently published which implies the use of recent radiation therapies (i.e. proton therapy and intensity modulated techniques rather than previously used conventional methods). Moreover, quantitative pooled estimates provided understandable importance level of the potential risk factors for developing cardiac events.

5. Conclusions

Current literatures provide important information about the necessity of incorporating patient and treatment factors for the prediction of cardiac toxicity after treatment of NSCLC patients. However, there is still a paucity of evidence presenting a reliable prediction model which could help clinicians to identify susceptible patients who should be protected from potential cardiac harms.

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Declaration of Competing Interest

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.

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Appendix A. Supplementary data

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