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Predicting mortalities among patients with acute aortic dissection: a methodological survey of published studies

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Abstract

Objective Limited efforts were available to systematically assess whether the published studies adequately addressed the prediction of mortality among patients with acute aortic dissection (AAD). Our study aimed to systematically review the methodological characteristics of studies that identified prognostic factors or developed or validated models for predicting mortalities among AAD patients, which would inform future work.

Design/setting a methodological survey of published studies.

Data source We searched PubMed and EMBASE for studies about prognostic factors or prediction models on mortality among AAD patients. Two reviewers independently collected the information about methodological characteristics. We also documented the information about the performance of the prognostic factors or prediction models.

Primary and secondary outcome measures Primary outcomes were all information about methodological characteristics. Secondary outcomes included the performance of the prognostic factors or prediction models.

Methods We searched PubMed and EMBASE for studies about prognostic factors or prediction models on mortality among AAD patients. Two reviewers independently collected the information about methodological characteristics. We also documented the information about the performance of the prognostic factors or prediction models.

Results Thirty-two studies were included, of which 18 evaluated the performance of prognostic factors, and 14 developed or validated prediction models. Of the 32 studies, 23 (72%) were single-center studies, 22 (69%) used data from electronic medical records, 19 (59%) chose retrospective cohort study design; 26 (81%) did not report missing predictor data, and five (16%) that reported missing predictor data used complete-case analysis. For the 14 prediction model studies, only three (21%) had the event per variable over 20, and only five (36%) reported both discrimination and calibration statistics. For model development studies, three (27%) did not report

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statistical methods, three (27%) exclusively used statistical significance threshold for selecting predictors, and seven (64%) did not report the methods for handling continuous predictors. The performance of prognostic factors showed varying discrimination (AUC 0.58 to 0.95), and the performance of prediction models also varied substantially (AUC 0.49 to 0.91). Only six studies reported calibration statistic.

Conclusions The methods used for prognostic studies on mortality among AAD patients -including prediction models or prognostic factor studies – were suboptimal, and the model performance highly varied. Substantial efforts are warranted to improve the use of the methods in this population.

Strengths and limitations of this study

- This systematic survey study is the first to identify methodological gaps among all studies addressing individual prognostic factors or developing or validating prediction models on mortality among AAD patients.
- This review is important that the methodological quality of models designed to support medical decision for AAD patients.
- It highlights substantial efforts are warranted to improve the use of the methods for better care of this population.
- Our survey about the methodological characteristics was primarily based on reporting.

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Introduction

Acute aortic dissection (AAD) is a life-threatening cardiovascular disease with high mortality, characterized with acute onset and rapid progression. The mortality of untreated AAD was approximately 1%-2% per hour early following the onset of symptoms, and the overall in-hospital mortality was approximately 27%.[1 2] Treatment options for AAD include medical intervention, surgery or endovascular repair, the selection of which mainly depends on complications and prognosis of patients.[3] Better understanding of the disease prognosis, ideally predicting the risk of a serious outcome, is highly desirable for medical decision making and patient communication, among which mortality has the highest priority.

Several published systematic reviews assessed the association of inflammatory biomarkers (e.g. C-reactive protein) and marker of cardiac injury (i.e. troponin) with increased morality in patients with AAD.[4-6] A few studies also developed or validated prediction models for mortality in AAD,[7-9] in which a combination of biomarkers, demographic and clinical characteristics were included.[8 10-14] As a result, they have received increasing use in clinical practice.

However, limited efforts have been made to systematically examine the performance of the prognostic factors or prediction models. In particular, a comprehensive assessment is strongly needed to investigate whether the published studies – either individual prognostic factor studies or prediction models – meet the desirable methodological rigors for clinical use, since suboptimal methods can compromise the accuracy and reliability of the risk estimation. This is particularly the case for AAD, a disease condition, whereby predictability of an adverse outcome has paramount importance. Therefore, we conducted a systematic survey study to identify methodological gaps among all studies addressing individual prognostic factors or developing or validating prediction models on mortality among AAD patients.

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Methods

Eligibility criteria

We developed the eligibility criteria under the PICOTS guidance.[15] A study was eligible for inclusion if it included patients diagnosed with AAD; and aimed to identify or assess any prognostic factors for morality, or develop or validate a prognostic model for mortality in AAD patients. We excluded a study if it was prediction model for AAD diagnosis only; or the report was a review, comment, letter or editorial, case report, protocol or conference abstract.

Predictors measured at any time point in the course of AAD were eligible. No restriction on study setting was applied; patients with AAD who visited any healthcare facilities were eligible. We defined a prognostic prediction model as a multivariable model, predicting risk of specific outcomes occurring in future by selected predictors.[16]

Literature search and screening

We searched PubMed and EMBASE from inception to June 2020 for relevant reports published in English language. We conducted the search using the MeSH terms and free texts to identify reports about AAD, including "aortic dissecting aneurysm", "aortic aneurysm", "aortic dissection*", and "aortic dissecting hematoma". We applied a validate search strategy for searching prediction models, which proved to have high sensitivity and specificity.[17] The full search strategy was presented as Appendix A. Two investigators (YR and SH) independently screened all searched reports, and resolved any disagreements through discussion with a third investigator (CL). We also manually searched for additional articles from the reference lists of all selected articles.

Data Extraction

We collected the following general information from each eligible study, including first author, year of publication, study aim, region of study, type of aortic dissection, age, sex ratio. We carefully collected information about performance of identified

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prognostic factors or prediction models, including their names and results about discrimination, calibration, sensitivity and specificity. Discrimination and calibration are the two key measures for evaluating the predictive performance of the prognostic factors or prediction models.[18]

In order to examine the methods used among these prognoses studies, a team of methods-trained, experienced methodologists expertise with prognostic studies and prediction models convened to develop a questionnaire through a consensus process. They firstly consulted items from the published statements and tools (e.g., PROBAST, CHARMS checklist) about prognoses studies,[19,20] and brainstormed for additional items. Subsequently, they discussed the identified items about their relevance for methods, and dropped items that were deemed irrelevant. Finally, they achieved consensus about the items through group discussion and agreement.

Generally, this questionnaire consists of five domains: (1) **study design** (number of centres, sample size, number of events, data sources, epidemiological design), (2) **participants** (definition and selection of participants); (3) **predictors** (definition and measurement of predictors); (4) **outcome** (definition and measurement of outcomes); (5) **analysis** (were all enrolled participants included in the analysis, the number of events per variable (EPV), statistical method for selecting and handling predictors, missing data, model structure used in the study, and relevant model performance measures evaluated for addressing prognostic factors or prediction models).

Statistical analysis

Categorical variables were expressed as the number of frequencies and proportion. For quantitative variables, data were summarized by mean and standard deviation or median with interquartile range according to normality tests.

Results

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In total, 13555 records were identified, among which 155 were selected for full-text screening, and 32 studies were eligible and included in the final analysis (Figure 1).

[Figure 1 here]

General characteristics of included studies

The 32 eligible studies were published between 2002 and 2019 (Appendix table 1). Five (15%) were multinational studies, and 21 (66%) were conducted in the USA, China, and Europe. The dissection type of AAD patients were mostly Type-A (n = 21, 66%), followed by a mixture of Type-A and Type-B (n = 8, 25%). In-hospital mortality was the most frequently used outcome (n = 24, 75%, Table 1).

Eighteen (56%) studies aimed to evaluate the performance of prognostic factors. The most commonly investigated prognostic factors were D-dimer (n = 8), NLR (n =4) and CRP (n = 3). Fourteen (44%) studies aimed to develop or validate a prediction model, of which nine developed a new prediction model without any validation, two developed a new prediction model with internal validation, and three conducted external validation with or without updating a prediction model (Table 1).

[Table 1 here]

Model performance

The performance of prognostic factors showed poor to strong discrimination (AUC 0.58 to 0.95). The AUC of single prognostic factor ranged from 0.58 to 0.92, and the one for combined prognostic factors ranged from 0.77 to 0.95 (DD and CRP: 0.95; NT-proBNP and aortic diameter: 0.83; TNC and D-dimer: 0.95; TNC and CRP: 0.91; cystatin C and hs-CRP:0.88; UA, D-dimer, and age: 0.77) (Table 2).

The developed or validated models from eleven studies showed poor to strong discrimination (AUC 0.49 to 0.91), only six reported calibrations, and of which five reported good calibrations. Rampoldi et al developed a prediction model and reported

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moderate discrimination (AUC 0.76). But through external validation, scoring systems developed by Rampoldi et al showed poor discrimination (30-day mortality: AUC 0.56, Operative mortality: AUC 0.62). Mehta et al (P value for the H-L test. =0.75) developed a prediction model using International Registry of Acute Aortic Dissection (IRAD) from multinational data and reported good calibration. Through external validation, IRAD score showed moderate discrimination (AUC 0.74), addition of CRP to IRAD score notably improved discrimination (AUC 0.89) (Table 2).

[Table 2 here]

Methodological characteristics

Among the 32 studies, most were single-center studies (n = 23, 72%). The sample size varied from 35 to 1034 (median 165, interquartile range, 103–348), and the median number of events was 35 (23–72). Thirteen (41%) studies used prospective cohort study design, and the rest 19 (59%) used retrospective cohort study design; 22 (69%) used data from electronic medical records (EMR), five (16%) from cohort studies, and five (16%) from registries.

Thirty-one (97%) studies clearly described inclusion and exclusion criteria. All studies used consistent criteria and measurement of the studied population. For the outcome, all but one study[13] used consistent criteria and measurement. For the analysis, 22 (69%) studies included all enrolled participants.

In the handling of missing data, 30 (94%) studies reported no missing outcome data; 26 (81%) did not report missing predictor data, and 5 (16%) reported that there were some predictors with missing data, and used complete-case analysis to handle missing predictors.

In 18 prognostic factor studies, nine (50%) had the events per variables (EPV) more than 20, eight (44%) between 10 and 20, and one (6%) less than 10; fifteen (83%)

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reported discrimination, sensitivity and specificity, other three (17%) only reported discrimination, or sensitivity and specificity; and 11 (61%) chose logistic regression model for the analysis, 5 (28%) used cox regression, 2 (11%) only used ROC analysis.

In the 14 prediction model studies, only three (21%) had the EPV more than 20, eight (57%) between 10 and 20, and three (21%) less than 10; 10 (71%) chose logistic regression model for the analysis, other four studies used cox regression, support vector machines, neural networks and ROC analysis respectively. The performance measures were poorly reported: only five (36%) reported both discrimination and calibration statistics. Eleven (64%) studies reported discrimination, measured as AUC of the receiver operated curve, and six (43%) reported calibration, measured as P value for the H-L test. For developing a prediction model, three (27%) did not report any statistical methods and three (27%) simply used statistical significance for selecting predictors; seven (64%) did not report how to handle continuous predictors, four (36%) reported continuous predictor was transformed into categories.

Discussion

In this systematic survey, we identified 32 studies addressing prognostic factors or prediction models for mortality among AAD patients. As noticed in this survey, the performance of prognostic factors or prediction models was most commonly evaluated by the AUC and H-L test. Most assessment of prognostic factors demonstrated moderate discrimination. The factors using combined TNC and D-dimer, or combined D-dimer and CRP showed strong discrimination (AUC 0.95). The prediction models showed poor to strong discrimination (AUC 0.49 to 0.91). The prediction model EuroSCORE II showed poor discriminative ability (AUC 0.49) and poor calibration (P value for the H-L test. <0.001). One explanation may be that EuroSCORE II is a risk model which allows the calculation of the risk of death after a heart surgery, and is not related to prognosis of patients with AAD, because not all patients with aortic dissection

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undergo surgical treatment, and some of them undergo endovascular treatment. Mehta et al.[7] model showed better discrimination (0.74) than the EuroSCORE II. Meanwhile, Mehta et al used IRAD from multinational data reported good calibration. Through external validation, IRAD score showed moderate discrimination (AUC 0.74), addition of CRP to IRAD score notably improved discrimination (AUC 0.89). Hence, the prediction model for mortality in AAD should consider including biomarkers as predictors to improve discrimination.

In this systematic survey, we found that most studies had small number of sample sizes and events, were derived from a single-center study, and a relatively large proportion of studies chose to use retrospective data. Most studies did not describe information on missing data nor accounted for appropriate statistical methods for handle missing data.

For developing or validating prediction models, we found that the number of EPV in most studies was relatively small, which result in prediction performance of models being possibly biased;[21 22] most studies did not evaluate both discrimination and calibration. Almost all studies reported discriminative ability of prediction models, while only six studies reported calibration. For developing prediction models, we found that some studies based on statistical significance for selecting variable may lead to suboptimal models; most studies did not report how to handle the continuous variable, and linear assumption may be inappropriate;

Although some studies showed good discrimination and calibration. Our findings highlighted important methodological limitations among those studies. Then it is possible that the result is not accurate and reliable. So in the future, studies about prognostic factors or prediction models for mortality in AAD should enroll large patient population from multicenter setting, meanwhile consider cohort designs, the imputation of missing data. Multiple imputation techniques to deal with missing data are important when evaluating model performance. Excluding cases with missing data may lead to biased results.[23]

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Studies about prediction models for mortality in AAD should consider appropriate methods for selecting variable and handling the continuous variable, and evaluating both discrimination and calibration. The number of participants and events should be planned, and the number of EPV should be at least 10. If the number of events is low relative to the number of predictors, penalized regression may be better than the standard regression. Stability selection and subsampling have demonstrated to yield more stable models based on a consistent selection of variables, so they should be used in future studies for prediction model.[24] Discrimination should not be reported in isolation because a poorly calibrated model can present the same discriminative capacity as a perfectly calibrated one.[25] Reporting both discrimination and calibration is highly recommended for evaluating performance measures. Validating the predictions models should be considered, as both model development and validation are essential processes for establishing a useful prediction model.[26]

To our knowledge, no systematic survey looking at the methodology characteristics and performance of prognostic factors or predictive models for mortality in AAD has been published. Whether these existing prognostic factors or prediction models may be used to guide or improve clinical practice remains underexplored. Should we seek better prognostic factors or prediction models? Should we continue using and validating these prognostic factors or prediction models? There is consensus on this issue among commentators. We should seek better prognostic factors or prediction models. Substantial efforts are warranted to strengthen the use of rigorous methods for the accuracy and reliability of the performance in the future research.

A limitation of the present study is that our survey about the methodological characteristics was primarily based on reporting. There might be cases that the researchers had considered the methodological issues but did not clearly report. This situation also emphasized the importance of complete reporting.

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Conclusions

In conclusion, D-dimer, NLR, and CRP predictors were the most commonly used biomarkers, the performance of prognostic factors showed a poor to strong discrimination, the prediction models varied substantially, only six studies reported the calibration, and of which five reported good calibration. Meanwhile, many of these prognostic factors or predictive models are weak methodologically, several important issues are needed to consider for strengthening for predicting mortality in AAD, such as the sample size, the methods for handling missing data, appropriate statistical analysis methods, and reporting both calibration and discrimination for prediction models. Substantial efforts are warranted to improve the use of the methods for better care of this population.

Contributors

Study concept and design: Yan Ren. Screening the articles: Yan Ren and Shiyao Huang. Acquisition of data: Yan Ren, Shiyao Huang and Chunrong Liu. Analysis of data: Yan Ren and Shiyao Huang. Drafting of the manuscript: Yan Ren. Writing - review & editing: Qianrui Li, Ling Li, Jing Tan, Kang Zou, and Xin Sun. Study supervision: Xin Sun.

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Competing Interests

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Patient consent for publication

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Ethics approval

The current study is a secondary analysis of the research data. No ethical approval was required for our study.

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Table 1. General characteristics about design and conduct of studies

Characteristics	Number (%)
Study region	
One country	27 (84.4)
China	14 (43.8)
USA	3 (9.4)
Europe	4 (12.5)
Other	5 (15.6)
Multinational	5 (15.6)
Multicenter study	
Yes	9 (28.1)
No	23 (71.9)
The most commonly reported prognostic biomarkers (n=18)	
D-dimer	8 (44.4)
NLR	4 (22.2)
CRP	3 (16.7)
Study purpose	
Identification or assessment of prognostic factors	18 (56.2)
Development or validation of a prediction models	14 (43.8)
Develop a model without validation	9 (28.1)
Develop a model internal validation	2 (6.3)
External validation	3 (9.4)
Dissection type	
A	21 (65.6)
B	3 (9.4)
A/B	8 (25.0)
Outcome (some studies have more than one outcome, such as in-hospital mortality and 1-year mortality)	
In-hospital mortality	24 (75.0)
Operative mortality	2 (6.25)
30-Day mortality	4 (12.5)
Long term mortality (included 1-year mortality)	5 (15.6)

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Table 2. Reported discrimination and calibration of prognostic factors or prediction models for acute aortic dissection

Study ID	Dissection type	Predictor	Outcome	AUC(95%CI)	P value of Hosmer-Lemeshow test	Sensitivity	Specificity
Prognostic factors							
Liu et al (2018a)[27]	A	Fibrinogen	In-hospital mortality	0.686 (0.585-0.787)		71.90%	60.40%
Zindovic et al (2018)[28]	A	Preoperative lactic acid levels	In-hospital mortality	0.684		56.00%	72.00%
			1-year mortality	0.673		48.00%	74.00%
		Postoperative lactic acid levels	In-hospital mortality	0.582			
			1-year mortality	0.498			
Oz et al (2017)[29]	A	NLR	In-hospital mortality	0.919 (0.832-1.00)		86.00%	91.00%
Feng et al (2017)[30]	A	serum cystatin C	Long-term mortality	0.772 (0.692–0.839)		78.53%	69.23%
		hs-CRP	(followed up for 909	0.640 (0.574–0.739)		86.72%	46.51%
		cystatin C, hs-CRP	days)	0.883 (0.826–0.935)		97.44%	65.92%
Li et al (2016)[11]	A	hs-TnT	Long-term mortality	0.719 (0.621-0.803)		70.80%	76.40%
		hs-CRP	(followed up for 3.5	0.700 (0.599-0.789)		48.90%	94.30%
		D-dimer	years)	0.818 (0.724-0.891)		86.10%	71.40%
Karakoyun et al (2015)[31]	A	NLR	In-hospital mortality	0.829 (0.674-0.984)		77.00%	74.00%
Wen et al (2019)[14]	A/B	NT-proBNP	In-hospital mortality	0.799 (0.707-0.891)		55.20%	95.70%
		Aortic diameter		0.724 (0.607-0.841)		58.60%	88.20%
		NT-proBNP and aortic diameter		0.832 (0.735-0.929)		79.30%	84.90%
Liu et al (2018b)[32]	A/B	BUN	In-hospital mortality	0.785 (0.662-0.909)		78.90%	72.20%
Bennett et al (2017)[33]	A	Serum lactic acid level	In-hospital mortality	0.88		85.00%	77.00%
			1-year mortality	0.81		67.00%	84.00%
LAFÇI et al (2014)[34]	A/B	NLR	In-hospital mortality	0.634 (0.516-0.753)		70.00%	53.00%
Wen et al (2013)[13]	A/B	D-dimer	In-hospital mortality	0.917 (0.85-0.96)		90.30%	75.90%

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		CRP		0.822 (0.74-0.89)	100.00%	54.20%
		D-dimer + CRP		0.948 (0.89-0.98)	81.90%	96.80%
Guo et al (2019)[10]	A/B	TNC	In-hospital mortality	0.884 (0.809-0.937)	83.87%	83.33%
		TNC + D-dimer		0.946 (0.885-0.980)	90.30%	88.46%
		D-dimer		0.787 (0.698-0.859)	87.19%	64.10%
		CRP		0.758 (0.667-0.835)	90.32%	55.13%
		TNC + CRP		0.909 (0.839-0.956)	90.32%	74.92%
Ohlmann et al (2006)[12]	A/B	D-dimer	In-hospital mortality	0.650 (0.584-0.716)		
Zhang et al (2016)[35]	A	WBC	In-hospital mortality		84.60%	65.90%
		SBP			65.90%	69.20%
		NT-proBNP			80.80%	51.20%
		D-dimer			84.60%	70.70%
Li et al (2019)[36]	B	PLR	In-hospital mortality	0.711 (0.580-0.840)	63.00%	88.00%
Zhang et al (2020)[37]	A	UA	In-hospital mortality	0.678 (0.579-0.777)	65.00%	67.10%
		D-dimer		0.689 (0.589-0.790)	44.70%	88.80%
		age		0.616 (0.507-0.724)	37.50%	90.40%
		UA, D-dimer, age		0.771		
Bedel et al (2019)[38]	A	NLR	In-hospital mortality	0.746 (0.623-0.870)	70.60%	76.80%
		PLR		0.750 (0.638-0.882)	76.50%	78.10%
Gong et al (2019)[39]	A	Postoperative TnI	30-Day mortality	0.711		
		Postoperative Mb		0.699		
		Preoperative CK-MB		0.694		
		Postoperative CK-MB		0.678		
		Preoperative Creatinine		0.668		
		Preoperative Mb		0.644		
		Preoperative D-Dimer		0.621		
		Preoperative TnI		0.618		
Prediction models						
Develop a model without validation						

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Zhang et al (2015)[40]	A/B	Hypotension, syncope, ischaemic complications, renal dysfunction, type A, neutrophil percentage ≥ 80%, surgery	In-hospital mortality	0.650	P=0.160		
Tolenaar et al (2014)[8]	B	Female, age, hypotension/ shock, periaortic hematoma, aortic diameter ≥5.5 cm, mesenteric ischemia, acute renal failure, limb ischemia	In-hospital mortality		P=0.314		
Mehta et al (2002)[7]	A	Age, female, abrupt onset pain, abnormal ECG, any pulse deficit, kidney failure, hypotension/shock/tamponade	In-hospital mortality	0.740	P=0.750		
Ghoreishi et al (2018)[41]	A	Lactic acid, creatinine, liver malperfusion	Operative mortality	0.750			
Centofanti et al (2006)[42]	A	Age, coma, acute renal failure, shock, and redo operation	30-Day mortality	Only reported the expected mortality and observed mortality			
Santini et al (2007)[43]	A	Age, cardiac tamponade, hypotension, acute myocardial ischemia, mesenteric ischemia, acute renal failure, neurologic injury	In-hospital mortality	0.763 (0.802-0.723)		55.60%	82.90%
Rampoldi et al (2007)[44]	A	Age > 70, history of aortic valve replacement, hypotension (systolic blood pressure < 100 mm Hg) or shock at presentation, migrating chest pain, preoperative cardiac tamponade, any pulse deficit, electrocardiogram with findings of myocardial ischemia or infarction	In-hospital mortality	0.760	P=0.230		
		Age > 70, history of aortic valve replacement, hypotension (systolic blood pressure < 100 mm Hg) or shock at presentation, migrating chest pain, preoperative cardiac tamponade, any pulse		0.810	P=0.380		

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		deficit, intraoperative hypotension, right ventricle dysfunction at surgery, a necessity to perform a coronary artery bypass graft					
Leontyev et al (2016)[45]	A	Age, Critical preoperative state, Malperfusion syndrome, Coronary artery disease	In-hospital mortality	0.767 (0.715-0.819)	=0.60		
Zhang et al (2019)[46]	B	Hypotension, Ischemic complications, Renal dysfunction, Neutrophil percentage	In-hospital mortality			86%(risk score≥4)	78%(risk score≥4)
Develop a model with internal validation							
Macrina et al (2010)[47]	A	immediate post-operative chronic renal failure, circulatory arrest time, the type of surgery on ascending aorta plus hemi-arch, extracorporeal circulation time and the presence of Marfan habitus	Long-term mortality (564±48 days)	Support vector machines:0.821, Neural networks: 0.870			
Macrina et al (2009)[48]	A	immediate post-operative presence of dialysis in continuous, renal complications, chronic renal failure, coded operative brain protection (anterograde better than retrograde perfusion), pre-operative neurological symptoms, age, previous cardiac surgery, the length of extracorporeal circulation, the operative presence of hemopericardium and postoperative enterological complications	30-Day mortality	First Centre: multiple logistic regression 0.879 (0.807-0. 932)			
		immediate post-operative presence of chronic renal failure, coded operative brain protection (anterograde better than retrograde perfusion), post-operative presence of dialysis in continuous, pre-operative neurological symptoms, post-operative renal complications, the length of extracorporeal circulation, age, the operative		Second Centre: multiple logistic regression 0.857 (C 0.785- 0.911) Second Centre: neural networks 0.905 (0.838 - 0.951)			

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		presence of hemopericardium, pre-operative presence of intubation, post-operative limb ischemia and enterological complications and the year of surgery					
External validation							
Ge et al (2013)[49]	A/B	EuroSCORE II	In-hospital mortality	0.490 (0.390-0.590)	< 0.001		
Yu et al (2016)[50]	A	Scoring systems developed by Rampoldi et al	Operative mortality	0.62			
			30-day mortality	0.56			
		Scoring systems developed by Centofanti et al	Operative mortality	0.66			
			30-day mortality	0.58			
		Age	Operative mortality	0.67			
Vrsalovic et al (2015)[9]	A	CRP	In-hospital mortality	0.790 (0.784-0.796)		83.00%	80.00%
		IRAD score		0.740 (0.733-0.747)			
		IRAD score + CRP		0.890 (0.886-0.894)			

NLR: neutrophil lymphocyte ratio; hs-TnT: high-sensitivity cardiac troponin T; hs-CRP: high-sensitivity C-reactive protein; IRAD score: international registry of acute aortic dissection score; CRP: C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; BUN: blood urea nitrogen; TNC: Tenascin-C; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; PLR: Platelet count to lymphocyte count ratio; CK-MB = creatine kinase MB isoenzyme; Mb= myoglobin.

Rampoldi et al were calculated for each patient as −3.20 + (0.68 × age > 70) + (1.44 × history of aortic valve replacement) + (1.17 × hypotension or shock at presentation) + (0.88 × migrating chest pain) + (0.97 × preoperative cardiac tamponade) + (0.56 × any pulse deficit) + (0.57 × electrocardiogram with findings of myocardial ischemia or infarction).

Centofanti et al were calculated for each patient as: −2.986 + (0.771 × shock) + (0.595 × reoperation) + (1.162 × coma) + (0.778 × acute renal failure) + (0.023 × age).

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Table 3. Methodological characteristics of included studies

Characteristics	Number (%) or median (interquartile range)
Sample size(n)	165 (103, 348)
Death events(n)	35 (23, 72)
Multicenter study	
Yes	9 (28.1)
No	23 (71.9)
Epidemiological design	
Prospective cohort	13 (40.6)
Retrospective cohort	19 (59.4)
Data sources	
Cohort study	5 (15.6)
EMR data	22 (68.8)
Registry	5 (15.6)
Whether did the study clearly describe inclusion/ exclusion criteria for participants	
Yes	31 (96.9)
No	1 (3.1)
Consistent definition/diagnostic criteria of predictors used in all participants	
Yes	32 (100.0)
No	0 (0)
Consistent measurement of predictors used in all participants	
Yes	32 (100.0)
No	0 (0)
Consistent definition/diagnostic criteria of outcomes used in all participants	
Yes	31 (96.9)
No	1 (3.1)
Consistent measurement of outcomes used in all participants	
Yes	31 (96.9)
No	1 (3.1)
Were all enrolled participants included in the analysis?	
Yes	22 (68.8)

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No	10 (31.2)
Was missing outcome data reported, and the methods handling missing outcome	
Yes, complete-case analysis	1 (3.1)
No	30 (93.8)
Not reported	1 (3.1)
Was any missing predictor data reported, and the methods handling missing predictor	
Yes, complete-case analysis	5 (15.6)
No	1 (3.1)
Not reported	26 (81.3)
Prognostic factors (n=18) prediction models	
Number of outcomes/events in relation to the number of predictors for assessing prognostic factors (Events Per Variable: EPVs)	
<10	1 (5.6)
10-20	8 (44.4)
≥20	9 (50.0)
Model structure used in the study	
Logistic regression	11 (61.1)
Cox regression	5 (27.8)
ROC analyses (Not report regression)	2 (11.1)
Relevant model performance measures evaluated for addressing prognostic factors	
AUC	2 (11.1)
AUC, sensitivity, specificity	15 (83.3)
Sensitivity, specificity	1 (5.6)
Prediction models (n=14)	
Number of outcomes/events in relation to the number of predictors in multivariable analysis (Events Per Variable: EPVs)	
<10	3 (21.4)
10-20	8 (57.1)
≥20	3 (21.4)
Model structure used in the study	
Logistic regression	10 (71.4)
Cox regression	1 (7.1)
ROC analyses (Not report regression)	1 (7.1)

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Logistic regression and support vector machines	1 (7.1)
Logistic regression and neural networks	1 (7.1)
Relevant model performance measures evaluated for addressing prediction models	
AUC, P value of Hosmer-Lemeshow test	5 (35.7)
AUC	4 (28.6)
AUC, sensitivity, specificity	2 (14.3)
P value of Hosmer-Lemeshow test	1 (7.1)
Expected and observed	1 (7.1)
Sensitivity, specificity	1 (7.1)
Develop prediction models (n=11)	
Statistical method for selecting predictors during addressing prediction models	
Univariate analysis of predictors by P value	3 (27.3)
Univariate analysis of predictors by P value and other specific predictors	3 (27.3)
Stepwise selection	2 (18.1)
Not reported	3 (27.3)
Handling the predictors for addressing prediction models	
Continuous predictor was transformed into categories	4 (36.4)
Not reported	7 (63.6)

EMR: electronic medical records

Figure 1. Flow chart of study selection

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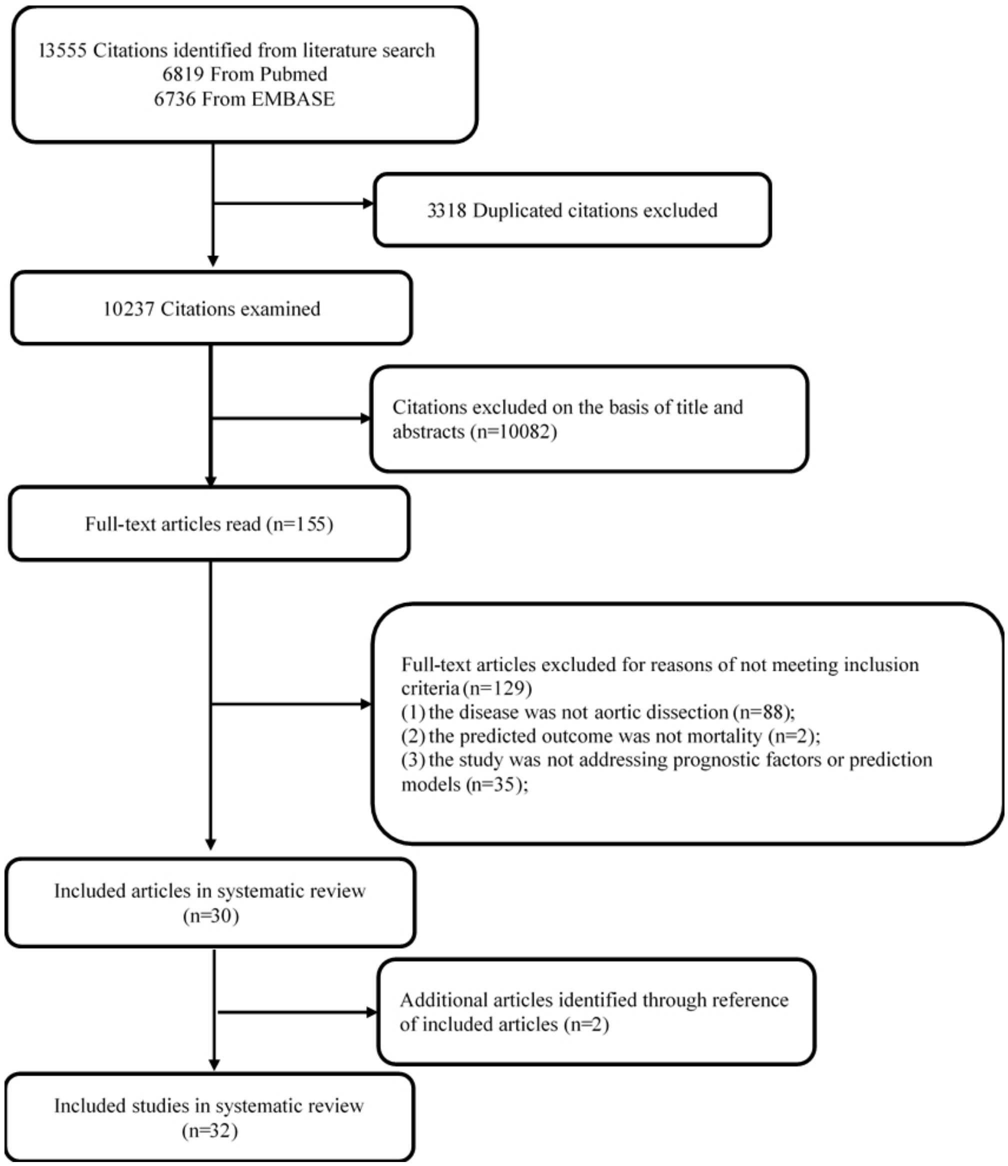

Figure 1. Flow chart of study selection

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Appendix A Search strategies

Database: PubMed (until June, 2020)
#1 (aortic dissecting aneurysm[MeSH Terms]) OR aortic dissecting aneurysm
#2 (aortic aneurysm[MeSH Terms]) OR aortic aneurysm
#3 (aortic dissection*[MeSH Terms]) OR aortic dissection*
#4 (aortic dissecting hematoma) OR aortic dissecting hematoma[MeSH Terms]
#5 #1 OR #2 OR #3 OR #4
#6 (validat* OR predict*[tiab] OR rule*) OR (predict* AND (outcome* OR risk* OR model*)) OR ((history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor*) AND (predict* OR model* OR decision* OR identif* OR prognos*)) OR (decision* AND (model* OR clinical* OR logistic models)) OR (prognostic AND (history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor* OR model*)) OR "stratification" OR "ROC Curve"[MeSH] OR "discrimination" OR "discriminate" OR "c statistic" OR "area under the curve" OR "AUC" OR "Calibration" OR "Indices" OR "algorithm" OR "Multivariable")
#7 ((cohort[MeSH Terms]) OR cohort) OR (observational[MeSH Terms]) OR observational) OR ((prospective[MeSH Terms]) OR prospective) OR((trial[MeSH Terms]) OR trial) OR ((epidemiology[MeSH Terms]) OR epidemiology) OR ((longitudinal[MeSH Terms]) OR longitudinal)
#8 #5 AND #6 AND #7
#9 (Animals[MeSH] NOT Humans[MeSH])
#10 #8 NOT #9
#11 English[Language]
#12 #10 AND #11
Database: EMBASE (until June, 2020)
#1 aortic dissecting aneurysm.mp. or exp dissecting aortic aneurysm/
#2 aortic aneurysm.mp. or exp aortic aneurysm/
#3 aortic dissection$.mp. or exp aortic dissection/
#4 exp aortic dissection/ or aortic dissecting hematoma.mp.
#5 #1 or #2 or #3 or #4
#6 exp cohort analysis/ or cohort.mp.
#7 exp observational study/ or observational.mp.
#8 prospective.mp. or exp prospective study/
#9 exp controlled clinical trial/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or trial.mp. or exp pragmatic trial/ or exp "controlled clinical trial (topic)"/ or exp clinical trial/ or exp adaptive clinical trial/ or exp randomized controlled trial/
#10 exp epidemiology/ or epidemiology.mp.
#11 exp longitudinal study/ or longitudinal.mp.
#12 #6 or #7 or #8 or #9 or #10
#13 (validat* or predict* or rule* or (predict* and (outcome* or risk* or model*)) or ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)) or (decision* and (model* or clinical* or logistic models)) or (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)) or ('stratification' or 'ROC Curve' or 'discrimination' or 'discriminate' or 'c statistic' or 'area under the curve' or 'AUC' or 'Calibration' or 'Indices' or 'algorithm' or 'Multivariable')).af.

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#14	#5 and #12 and #13
#15	limit #14 to (human and english language)

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Appendix Table 1. General characteristics of studies included in the systematic review

Study ID	Region	Period of Data Collection	Centers (n)	Sample size for analysis (n)	Event	Study design	Data sources	Age (Mean±SD or median (interquartile range)) (years)	Male (%)	Study purpose
Liu et al (2018a)	China	2006.01-2017.01	1	143	32	Retrospective cohort	EMR data	5[illegible].6 (43.0, 62.0)	72.00%	Prediction performance of prognostic factors
Zindovic et al (2018)	Sweden	2005.01-2017.02	1	277	37	Retrospective cohort	EMR data	63.[illegible]±11.4	63.86%	Prediction performance of prognostic factors
Oz et al (2017)	Turkey		1	57	15	Retrospective cohort	EMR data	5[illegible].[illegible]±10.5	15.80%	Prediction performance of prognostic factors
Li et al (2016)	China	2010.05-2014.06	4	103	36	Prospective cohort	EMR data	54.[illegible]±13.4	68.93%	Prediction performance of prognostic factors
Vrsalovic et al (2015)	Croatia	2006.01-2013.12	1	54	24	Retrospective cohort	EMR data	69.[illegible]±14.0	63.00%	External validation
Karakoyun et al (2015)	Turkey	2009-2013	1	35	9	Retrospective cohort	EMR data	55.91±7.95	80.00%	Prediction performance of prognostic factors
Wen et al (2019)	China	2008.03-2012.01	1	122	29	Prospective cohort	Cohort	50.0[illegible]±8.35	84.43%	Prediction performance of prognostic factors
Liu et al (2018b)	China	2012.12-2016.06	1	192	19	Retrospective cohort	EMR data	5[illegible].0 (4[illegible].0, 62.0)	78.60%	Prediction performance of prognostic factors
Bennett et al (2017)	USA	2000-2014	1	144	38	Retrospective cohort	EMR data	58.7 (4[illegible].9, 69.7)	67.00%	Prediction performance of prognostic factors
Zhang et al (2015)	China	2008.01-2013.10	1	360	77	Prospective cohort	Cohort	57.1±12.6	75.80%	Develop a model without validation

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LAFÇI et al (2014)	Turkey	2007.01-2012.01	1	104	33		Retrospective cohort	EMR data	55.[illegible]±14.0	73.08%	Prediction performance of prognostic factors
Wen et al (2013)	China	2007.01-2011.10	1	114	31		Prospective cohort	Cohort	[illegible]8.[illegible]±7.6	84.20%	Prediction performance of prognostic factors
Guo et al (2019)	China	2015.12-2017.08	1	109	31		Prospective cohort	Cohort	[illegible]2.[illegible]±12.3	59.63%	Prediction performance of prognostic factors
Ohlmann et al (2006)	France	1997.01-2003.12	1	93	22		Retrospective cohort	EMR data	[illegible]3.[illegible]±12.6	66.00%	Prediction performance of prognostic factors
Ge et al (2013)	China	2009.02-2012.02	1	384	31		Retrospective cohort	Cohort	4[illegible].[illegible]±10.8	20.05%	External Validation
Tolenaar et al (2014)	Multinational	1996.01-2013.04	Multicenter	1034	110		Prospective cohort	Registry	63.[illegible]±14.0	65.10%	Develop a model without validation
Mehta et al (2002)	6 countries	1996.01-1999.12	18	547	178		Prospective cohort	Registry	61.[illegible]±14.1	65.50%	Develop a model without validation
Yu et al (2016)	USA	2008-2013	1	79	13		Retrospective cohort	EMR data	[illegible]0(interquartile range: 51-70)	65.80%	External validation
Feng et al (2017)	China	2010.02-2014.12	1	136	39		Prospective cohort	EMR data	53.[illegible]±10.3	56.60%	Prediction performance of prognostic factors
Ghoreishi et al (2018)	USA	2002.01-2015.12	1	269		43	Retrospective cohort	EMR data	5[illegible]±14	67.00%	Develop a model without validation
Zhang et al (2016)	China	2014.01-2015.06	1	67		26	Retrospective cohort	EMR data			Prediction performance of prognostic factors
Macrina et al (2010)	Italy	2002.01-late 2008	2	235		84	Prospective cohort	EMR data			Develop a model with internal validation
Macrina et al (2009)	Italy	2001.01-early 2008	2	208		53	Prospective cohort	EMR data	Survivors:61±12; Nonsurvivors: 6[illegible]±10	64.00%	Develop a model with internal validation

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Li et al (2019)	China	2007-2013.08	1	134	19	Prospective cohort	EMR data	Men: 50.59 ± 13.70, Women: 52.17 ± 1[illegible].55	67.3%	Prediction performance of prognostic factors
Centofanti et al (2006)	Multinational	1980-2004	Multicenter	616	154	Prospective cohort	Registry			Develop a model without validation
Santini et al (2007)		1979-2004		311	72	Retrospective cohort	EMR data	[illegible]9.5 ± 13	72.00%	Develop a model without validation
Rampoldi et al (2007)	Multinational	1996-2003	18	682	163	Retrospective cohort	Registry	5[illegible].9 ± 13.8	70.30%	Develop a model without validation
Leontyev et al (2016)	Multinational	1996-2011	2	534	100	Prospective cohort	Registry	6[illegible] ± 14	63.70%	Develop a model without validation
Zhang et al (2019)	China	2013.11.01-2016.10.30	1	188	17	Prospective cohort	EMR data	57.[illegible] ± 12.6	77.10%	Develop a model without validation
Zhang et al (2020)	China	2016.01-2019.06	1	186	40	Retrospective cohort	EMR data	50[illegible] ± 12	80.00%	Prediction performance of prognostic factors
Bedel et al (2019)	Finland	2013.01-2018.06	1	96	17	Retrospective cohort	EMR data	63.[illegible]±13.4	81.20%	Prediction performance of prognostic factors
Gong et al (2019)	China	2015.01-2017.05	1	583	70	Retrospective cohort	EMR data	48.05 ± 11.29		Prediction performance of prognostic factors

NLR: neutrophil lymphocyte ratio; hs-TnT: high-sensitivity cardiac troponin T; hs-CRP: high-sensitivity C-reactive protein; IRAD score: international registry of acute aortic dissection score; CRP: C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; BUN: blood urea nitrogen; TNC: Tenascin-C; EuroSCORE II: European System for Cardiac Operative Risk Evaluation.

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Prognostic factors and prediction models for acute aortic dissection: a systematic review

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Abstract

Objective Our study aimed to systematically review the methodological characteristics of studies that identified prognostic factors or developed or validated models for predicting mortalities among AAD patients, which would inform future work.

Design/setting a methodological review of published studies.

Methods We searched PubMed and EMBASE from inception to June 2020 for studies about prognostic factors or prediction models on mortality among AAD patients. Two reviewers independently collected the information about methodological characteristics. We also documented the information about the performance of the prognostic factors or prediction models.

Results Thirty-two studies were included, of which 18 evaluated the performance of prognostic factors, and 14 developed or validated prediction models. Of the 32 studies, 23 (72%) were single-center studies, 22 (69%) used data from electronic medical records, 19 (59%) chose retrospective cohort study design; 26 (81%) did not report missing predictor data, and five (16%) that reported missing predictor data used complete-case analysis. Among the 14 prediction model studies, only three (21%) had the event per variable over 20, and only five (36%) reported both discrimination and calibration statistics. Among model development studies, three (27%) did not report statistical methods, three (27%) exclusively used statistical significance threshold for selecting predictors, and seven (64%) did not report the methods for handling continuous predictors. Most prediction models were considered at high risk of bias. The performance of prognostic factors showed varying discrimination (AUC 0.58 to 0.95), and the performance of prediction models also varied substantially (AUC 0.49 to 0.91). Only six studies reported calibration statistic.

Conclusions The methods used for prognostic studies on mortality among AAD patients -including prediction models or prognostic factor studies – were suboptimal, and the model performance highly varied. Substantial efforts are warranted to improve the use of the methods in this population.

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Strengths and limitations of this study

- This systematic review study is the first to identify methodological gaps and assess the performance of the prognostic factors or prediction models among all studies addressing individual prognostic factors or developing or validating prediction models on mortality among AAD patients.
- This review designed a comprehensive questionnaire that included items from both PROBAST and CHARMS checklists and assessed methodological gaps among all studies.
- This review is important that the methodological quality of models designed to support medical decision for AAD patients, substantial efforts are warranted to strengthen the use of rigorous methods for the accuracy and reliability of the performance in the future research.
- The small number of prediction models limit the recommendation in clinical practice, combining IRAD score and CRP model showed better discrimination than IRAD score, future studies may consider updating IRAD model by including other relevant biomarkers, which may further improve prognostic performance.
- Our review about the methodological characteristics was primarily based on reporting, which might be cases that the researchers had considered the methodological issues but did not clearly report.

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Introduction

Acute aortic dissection (AAD) is a life-threatening cardiovascular disease with high mortality, characterized with acute onset and rapid progression. The mortality of untreated AAD was approximately 1%-2% per hour early following the onset of symptoms, and the overall in-hospital mortality was approximately 27%.[1 2] Treatment options for AAD include medical intervention, surgery or endovascular repair, the selection of which mainly depends on complications and prognosis of patients.[3] Better understanding of the disease prognosis, ideally predicting the risk of a serious outcome, is highly desirable for medical decision making and patient communication, among which mortality has the highest priority.

Several published systematic reviews assessed the association of inflammatory biomarkers (e.g. C-reactive protein) and marker of cardiac injury (i.e. troponin) with increased mortality in patients with AAD.[4-6] A few studies also developed or validated prediction models for mortality in AAD,[7-9] in which a combination of biomarkers, demographic and clinical characteristics were included.[8 10-14] As a result, they have received increasing use in clinical practice.

However, limited efforts have been made to systematically examine the performance of the prognostic factors or prediction models. In particular, a comprehensive assessment is strongly needed to investigate whether the published studies – either individual prognostic factor studies or prediction models – meet the desirable methodological rigors for clinical use, since suboptimal methods can compromise the accuracy and reliability of the risk estimation. This is particularly the case for AAD, a disease condition, whereby predictability of an adverse outcome has paramount importance. Therefore, we conducted a systematic review study to identify methodological gaps among all studies addressing individual prognostic factors or developing or validating prediction models on mortality among AAD patients.

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Methods

We conducted this systematic review according to a pre-specified protocol, which was not published.

Eligibility criteria

We developed the eligibility criteria under the PICOTS guidance.[15] A study was eligible for inclusion if it included patients diagnosed with AAD; and aimed to identify or assess any prognostic factors for mortality, or develop or validate a prognostic model for mortality in AAD patients. We excluded a study if it was prediction model for AAD diagnosis only; or the report was a review, comment, letter or editorial, case report, protocol or conference abstract.

Predictors measured at any time point in the course of AAD were eligible. No restriction on study setting was applied; patients with AAD who visited any healthcare facilities were eligible. We defined a prognostic prediction model as a multivariable model, predicting risk of specific outcomes occurring in future by selected predictors.[16]

Literature search and screening

We searched PubMed and EMBASE from inception to June 2020 for relevant reports published in English language. We conducted the search using the MeSH terms and free texts to identify reports about AAD, including “aortic dissecting aneurysm”, “aortic aneurysm”, “aortic dissection*”, and “aortic dissecting hematoma”. We applied a validate search strategy for searching prediction models, which proved to have high sensitivity and specificity.[17] The full search strategy was presented as Appendix A. Two investigators (YR and SH) independently screened all searched reports, and resolved any disagreements through discussion with a third investigator (CL). We also manually searched for additional articles from the reference lists of all selected articles.

Data Extraction

We collected the following general information from each eligible study, including first

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author, year of publication, study aim, region of study, type of aortic dissection, age, sex ratio. We carefully collected information about performance of identified prognostic factors or prediction models, including their names and results about discrimination, calibration, sensitivity and specificity. Discrimination and calibration are the two key measures for evaluating the predictive performance of the prognostic factors or prediction models.[18]

In order to examine the methods used among these prognoses studies, a team of methods-trained, experienced methodologists expertise with prognostic studies and prediction models convened to develop a questionnaire through a consensus process. They firstly consulted items from the published statements and tools (e.g., PROBAST, CHARMS checklist) about prognoses studies,[19,20] and brainstormed for additional items. Subsequently, they discussed the identified items about their relevance for methods, and dropped items that were deemed irrelevant. Finally, they achieved consensus about the items through group discussion and agreement.

Generally, this questionnaire consists of five domains: (1) **study design** (number of centres, sample size, number of events, data sources, epidemiological design), (2) **participants** (definition and selection of participants); (3) **predictors** (definition and measurement of predictors); (4) **outcome** (definition and measurement of outcomes); (5) **analysis** (were all enrolled participants included in the analysis, the number of events per variable (EPV), statistical method for selecting and handling predictors, missing data, model structure used in the study, and relevant model performance measures evaluated for addressing prognostic factors or prediction models). The questionnaire was presented as Appendix B.

Additionally, we used a risk of bias assessment tool adapted from the PROBAST tool to assess the risk of bias for prediction modelling studies.[15,20] The detailed tool and assessment criteria were presented in Appendix C.

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Statistical analysis

Categorical variables were expressed as the number of frequencies and proportion. For quantitative variables, data were summarized by mean and standard deviation or median with interquartile range according to normality tests.

Results

In total, 13555 records were identified, among which 155 were selected for full-text screening, and 32 studies were eligible and included in the final analysis (Figure 1).

[Figure 1 here]

General characteristics of included studies

The 32 eligible studies were published between 2002 and 2019 (Appendix table 1). Five (15%) were multinational studies, and 21 (66%) were conducted in the USA, China, and Europe. The dissection type of AAD patients were mostly Type-A (n = 21, 66%), followed by a mixture of Type-A and Type-B (n = 8, 25%). In-hospital mortality was the most frequently used outcome (n = 24, 75%) (Table 1).

Eighteen (56%) studies aimed to evaluate the performance of prognostic factors. The most commonly investigated prognostic factors were D-dimer (n = 8), NLR (n =4) and CRP (n = 3). Fourteen (44%) studies aimed to develop or validate a prediction model, of which nine developed a new prediction model without any validation, two developed a new prediction model with internal validation, and three conducted external validation with or without updating a prediction model (Table 1).

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Table 1. General characteristics about design and conduct of studies

Characteristics	Number (%)
Study region	
One country	27 (84.4)
China	14 (43.8)
USA	3 (9.4)
Europe	4 (12.5)
Other	5 (15.6)
Multinational	5 (15.6)
Multicenter study	
Yes	9 (28.1)
No	23 (71.9)
The most commonly reported prognostic biomarkers (n=18)	
D-dimer	8 (44.4)
NLR	4 (22.2)
CRP	3 (16.7)
Study purpose	
Identification or assessment of prognostic factors	18 (56.2)
Development or validation of a prediction models	14 (43.8)
Develop a model without validation	9 (28.1)
Develop a model internal validation	2 (6.3)
External validation	3 (9.4)
Dissection type	
A	21 (65.6)
B	3 (9.4)
A/B	8 (25.0)
Outcome (some studies have more than one outcome, such as in-hospital mortality and 1-year mortality)	
In-hospital mortality	24 (75.0)
Operative mortality	2 (6.25)
30-Day mortality	4 (12.5)
Long term mortality (included 1-year mortality)	5 (15.6)

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Model performance

The performance of prognostic factors showed poor to strong discrimination (AUC 0.58 to 0.95). The AUC of single prognostic factor ranged from 0.58 to 0.92, and the one for combined prognostic factors ranged from 0.77 to 0.95 (DD and CRP: 0.95; NT-proBNP and aortic diameter: 0.83; TNC and D-dimer: 0.95; TNC and CRP: 0.91; cystatin C and hs-CRP:0.88; UA, D-dimer, and age: 0.77) (Table 2).

The developed or validated models from eleven studies showed poor to strong discrimination (AUC 0.49 to 0.91), only six reported calibrations, and of which five reported good calibrations (P>0.05). Rampoldi et al developed a prediction model and reported moderate discrimination (AUC 0.76). But through external validation, scoring systems developed by Rampoldi et al showed poor discrimination (30-day mortality: AUC 0.56, Operative mortality: AUC 0.62). Mehta et al (P value for the H-L test. =0.75) developed a prediction model using International Registry of Acute Aortic Dissection (IRAD) from multinational data and reported good calibration. Through external validation, IRAD score showed moderate discrimination (AUC 0.74), addition of CRP to IRAD score notably improved discrimination (AUC 0.89) (Table 2).

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Table 2. Reported discrimination and calibration of prognostic factors or prediction models for acute aortic dissection

Study ID	Dissection type	Predictor	Outcome	AUC(95%CI)	P value of Hosmer-Lemeshow test	Sensitivity	Specificity
Prognostic factors							
Liu et al (2018a)[21]	A	Fibrinogen	In-hospital mortality	0.686 (0.585-0.787)		71.90%	60.40%
Zindovic et al (2018)[22]	A	Preoperative lactic acid levels	In-hospital mortality	0.684		56.00%	72.00%
			1-year mortality	0.673		48.00%	74.00%
		Postoperative lactic acid levels	In-hospital mortality	0.582			
			1-year mortality	0.498			
Oz et al (2017)[23]	A	NLR	In-hospital mortality	0.919 (0.832-1.00)		86.00%	91.00%
Feng et al (2017)[24]	A	serum cystatin C	Long-term mortality (followed up for 909 days)	0.772 (0.692–0.839)		78.53%	69.23%
		hs-CRP		0.640 (0.574–0.739)		86.72%	46.51%
		cystatin C, hs-CRP		0.883 (0.826–0.935)		97.44%	65.92%
Li et al (2016)[11]	A	hs-TnT	Long-term mortality (followed up for 3.5 years)	0.719 (0.621-0.803)		70.80%	76.40%
		hs-CRP		0.700 (0.599-0.789)		48.90%	94.30%
		D-dimer		0.818 (0.724-0.891)		86.10%	71.40%
Karakoyun et al (2015)[25]	A	NLR	In-hospital mortality	0.829 (0.674-0.984)		77.00%	74.00%
Wen et al (2019)[14]	A/B	NT-proBNP	In-hospital mortality	0.799 (0.707-0.891)		55.20%	95.70%
		Aortic diameter		0.724 (0.607-0.841)		58.60%	88.20%
		NT-proBNP and aortic diameter		0.832 (0.735-0.929)		79.30%	84.90%
Liu et al (2018b)[26]	A/B	BUN	In-hospital mortality	0.785 (0.662-0.909)		78.90%	72.20%
Bennett et al (2017)[27]	A	Serum lactic acid level	In-hospital mortality	0.88		85.00%	77.00%
			1-year mortality	0.81		67.00%	84.00%
LAFÇI et al (2014)[28]	A/B	NLR	In-hospital mortality	0.634 (0.516-0.753)		70.00%	53.00%
Wen et al (2013)[13]	A/B	D-dimer	In-hospital mortality	0.917 (0.85-0.96)		90.30%	75.90%

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		CRP		0.822 (0.74-0.89)	100.00%	54.20%
		D-dimer + CRP		0.948 (0.89-0.98)	81.90%	96.80%
Guo et al (2019)[10]	A/B	TNC	In-hospital mortality	0.884 (0.809-0.937)	83.87%	83.33%
		TNC + D-dimer		0.946 (0.885-0.980)	90.30%	88.46%
		D-dimer		0.787 (0.698-0.859)	87.19%	64.10%
		CRP		0.758 (0.667-0.835)	90.32%	55.13%
		TNC + CRP		0.909 (0.839-0.956)	90.32%	74.92%
Ohlmann et al (2006)[12]	A/B	D-dimer	In-hospital mortality	0.650 (0.584-0.716)		
Zhang et al (2016)[29]	A	WBC	In-hospital mortality		84.60%	65.90%
		SBP			65.90%	69.20%
		NT-proBNP			80.80%	51.20%
		D-dimer			84.60%	70.70%
Li et al (2019)[30]	B	PLR	In-hospital mortality	0.711 (0.580-0.840)	63.00%	88.00%
Zhang et al (2020)[31]	A	UA	In-hospital mortality	0.678 (0.579-0.777)	65.00%	67.10%
		D-dimer		0.689 (0.589-0.790)	44.70%	88.80%
		age		0.616 (0.507-0.724)	37.50%	90.40%
		UA, D-dimer, age		0.771		
Bedel et al (2019)[32]	A	NLR	In-hospital mortality	0.746 (0.623-0.870)	70.60%	76.80%
		PLR		0.750 (0.638-0.882)	76.50%	78.10%
Gong et al (2019)[33]	A	Postoperative TnI	30-Day mortality	0.711		
		Postoperative Mb		0.699		
		Preoperative CK-MB		0.694		
		Postoperative CK-MB		0.678		
		Preoperative Creatinine		0.668		
		Preoperative Mb		0.644		
		Preoperative D-Dimer		0.621		
		Preoperative TnI		0.618		
Prediction models						
Develop a model without validation						

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Zhang et al (2015)[34]	A/B	Hypotension, syncope, ischaemic complications, renal dysfunction, type A, neutrophil percentage ≥ 80%, surgery	In-hospital mortality	0.650	0.160		
Tolenaar et al (2014)[8]	B	Female, age, hypotension/ shock, periaortic hematoma, aortic diameter ≥5.5 cm, mesenteric ischemia, acute renal failure, limb ischemia	In-hospital mortality		P=0.314		
Mehta et al (2002)[7]	A	Age, female, abrupt onset pain, abnormal ECG, any pulse deficit, kidney failure, hypotension/shock/tamponade	In-hospital mortality	0.740	P=0.750		
Ghoreishi et al (2018)[35]	A	Lactic acid, creatinine, liver malperfusion	Operative mortality	0.750			
Centofanti et al (2006)[36]	A	Age, coma, acute renal failure, shock, and redo operation	30-Day mortality	Only reported the expected mortality and observed mortality			
Santini et al (2007)[37]	A	Age, cardiac tamponade, hypotension, acute myocardial ischemia, mesenteric ischemia, acute renal failure, neurologic injury	In-hospital mortality	0.763 (0.802-0.723)		55.60%	82.90%
Rampoldi et al (2007)[38]	A	Age > 70, history of aortic valve replacement, hypotension (systolic blood pressure < 100 mm Hg) or shock at presentation, migrating chest pain, preoperative cardiac tamponade, any pulse deficit, electrocardiogram with findings of myocardial ischemia or infarction	In-hospital mortality	0.760	P=0.230		
		Age > 70, history of aortic valve replacement, hypotension (systolic blood pressure < 100 mm Hg) or shock at presentation, migrating chest pain, preoperative cardiac tamponade, any pulse		0.810	P=0.380		

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		deficit, intraoperative hypotension, right ventricle dysfunction at surgery, a necessity to perform a coronary artery bypass graft					
Leontyev et al (2016)[39]	A	Age, Critical preoperative state, Malperfusion syndrome, Coronary artery disease	In-hospital mortality	0.767 (0.715-0.819)	=0.60		
Zhang et al (2019)[40]	B	Hypotension, Ischemic complications, Renal dysfunction, Neutrophil percentage	In-hospital mortality			86%(risk score≥4)	78%(risk score≥4)
Develop a model with internal validation							
Macrina et al (2010)[41]	A	immediate post-operative chronic renal failure, circulatory arrest time, the type of surgery on ascending aorta plus hemi-arch, extracorporeal circulation time and the presence of Marfan habitus	Long-term mortality (564±48 days)	Support vector machines:0.821, Neural networks: 0.870			
Macrina et al (2009)[42]	A	immediate post-operative presence of dialysis in continuous, renal complications, chronic renal failure, coded operative brain protection (anterograde better than retrograde perfusion), pre-operative neurological symptoms, age, previous cardiac surgery, the length of extracorporeal circulation, the operative presence of hemopericardium and postoperative enterological complications	30-Day mortality	First Centre: multiple logistic regression 0.879 (0.807-0. 932)			
		immediate post-operative presence of chronic renal failure, coded operative brain protection (anterograde better than retrograde perfusion), post-operative presence of dialysis in continuous, pre-operative neurological symptoms, post-operative renal complications, the length of extracorporeal circulation, age, the operative		Second Centre: multiple logistic regression 0.857 (CIs 0.785- 0.911) Second Centre: neural networks 0.905 (0.838 - 0.951)			

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		presence of hemopericardium, pre-operative presence of intubation, post-operative limb ischemia and enterological complications and the year of surgery					
External validation							
Ge et al (2013)[43]	A/B	EuroSCORE II	In-hospital mortality	0.490 (0.390-0.590)	< 0.001		
Yu et al (2016)[44]	A	Scoring systems developed by Rampoldi et al	Operative mortality	0.62			
			30-day mortality	0.56			
		Scoring systems developed by Centofanti et al	Operative mortality	0.66			
			30-day mortality	0.58			
		Age	Operative mortality	0.67			
Vrsalovic et al (2015)[9]	A	CRP	In-hospital mortality	0.790 (0.784-0.796)		83.00%	80.00%
		IRAD score		0.740 (0.733-0.747)			
		IRAD score + CRP		0.890 (0.886-0.894)			

NLR: neutrophil lymphocyte ratio; hs-TnT: high-sensitivity cardiac troponin T; hs-CRP: high-sensitivity C-reactive protein; IRAD score: international registry of acute aortic dissection score; CRP: C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; BUN: blood urea nitrogen; TNC: Tenascin-C; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; PLR: Platelet count to lymphocyte count ratio; CK-MB = creatine kinase MB isoenzyme; Mb= myoglobin.

Rampoldi et al were calculated for each patient as $-3.20 + (0.68 \times \text{age} > 70) + (1.44 \times \text{history of aortic valve replacement}) + (1.17 \times \text{hypotension or shock at presentation}) + (0.88 \times \text{migrating chest pain}) + (0.97 \times \text{preoperative cardiac tamponade}) + (0.56 \times \text{any pulse deficit}) + (0.57 \times \text{electrocardiogram with findings of myocardial ischemia or infarction})$.

Centofanti et al were calculated for each patient as: $-2.986 + (0.771 \times \text{shock}) + (0.595 \times \text{reoperation}) + (1.162 \times \text{coma}) + (0.778 \times \text{acute renal failure}) + (0.023 \times \text{age})$.

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Methodological characteristics

Among the 32 studies, most were single-center studies (n = 23, 72%). The sample size varied from 35 to 1034 (median 165, interquartile range, 103–348), and the median number of events was 35 (23–72). Thirteen (41%) studies used prospective cohort study design, and the rest 19 (59%) used retrospective cohort study design; 22 (69%) used data from electronic medical records (EMR), five (16%) from cohort studies, and five (16%) from registries (Table 3).

Thirty-one (97%) studies clearly described inclusion and exclusion criteria for participants. The criteria used to define and to measure predictors in the study population were consistent among all included studies. The criteria for outcome definition and measurement was consistent in all but one study[13]. (Table 3).

22 (69%) studies included all enrolled participants in the analysis. In the handling of missing data, 30 (94%) studies reported no missing outcome data; 26 (81%) did not report missing predictor data, and 5 (16%) reported that there were some predictors with missing data, and used complete-case analysis to handle missing predictors (Table 3).

In 18 prognostic factor studies, nine (50%) had the events per variables (EPV) more than 20, eight (44%) between 10 and 20, and one (6%) less than 10; fifteen (83%) reported discrimination, sensitivity and specificity, other three (17%) only reported discrimination, or sensitivity and specificity; and 11 (61%) chose logistic regression model for the analysis, 5 (28%) used cox regression, 2 (11%) only used ROC analysis (Table 3).

In the 14 prediction model studies, only three (21%) had the EPV more than 20, eight (57%) between 10 and 20, and three (21%) less than 10; 10 (71%) chose logistic regression model for the analysis, other four studies used cox regression, support vector

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machines, neural networks and ROC analysis respectively. The performance measures were poorly reported: only five (36%) reported both discrimination and calibration statistics. Eleven (64%) studies reported discrimination, measured as AUC of the receiver operated curve, and six (43%) reported calibration, measured as P value for the H-L test. For developing a prediction model, three (27%) did not report any statistical methods and three (27%) simply used statistical significance for selecting predictors; seven (64%) did not report how to handle continuous predictors, four (36%) reported continuous predictor was transformed into categories (Table 3).

Table 3. Methodological characteristics of included studies

Characteristics	**Number (%) or median (interquartile range)**
Sample size(n)	165 (103, 348)
Death events(n)	35 (23, 72)
Multicenter study	
Yes	9 (28.1)
No	23 (71.9)
Epidemiological design	
Prospective cohort	13 (40.6)
Retrospective cohort	19 (59.4)
Data sources	
Cohort study	5 (15.6)
EMR data	22 (68.8)
Registry	5 (15.6)
Whether did the study clearly describe inclusion/ exclusion criteria for participants	
Yes	31 (96.9)
No	1 (3.1)
Consistent definition/diagnostic criteria of predictors used in all participants	
Yes	32 (100.0)
No	0 (0)
Consistent measurement of predictors used in all participants	
Yes	32 (100.0)
No	0 (0)

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Consistent definition/diagnostic criteria of outcomes used in all participants	
Yes	31 (96.9)
No	1 (3.1)
Consistent measurement of outcomes used in all participants	
Yes	31 (96.9)
No	1 (3.1)
Were all enrolled participants included in the analysis?	
Yes	22 (68.8)
No	10 (31.2)
Was missing outcome data reported, and the methods handling missing outcome	
Yes, complete-case analysis	1 (3.1)
No	30 (93.8)
Not reported	1 (3.1)
Was any missing predictor data reported, and the methods handling missing predictor	
Yes, complete-case analysis	5 (15.6)
No	1 (3.1)
Not reported	26 (81.3)
Prognostic factors (n=18) prediction models	
Number of outcomes/events in relation to the number of predictors for assessing prognostic factors (Events Per Variable: EPVs)	
<10	1 (5.6)
10-20	8 (44.4)
≥20	9 (50.0)
Model structure used in the study	
Logistic regression	11 (61.1)
Cox regression	5 (27.8)
ROC analyses (Not report regression)	2 (11.1)
Relevant model performance measures evaluated for addressing prognostic factors	
AUC	2 (11.1)
AUC, sensitivity, specificity	15 (83.3)
Sensitivity, specificity	1 (5.6)

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Prediction models (n=14)	
Number of outcomes/events in relation to the number of predictors in multivariable analysis (Events Per Variable: EPVs)	
<10	3 (21.4)
10-20	8 (57.1)
≥20	3 (21.4)
Model structure used in the study	
Logistic regression	10 (71.4)
Cox regression	1 (7.1)
ROC analyses (Not report regression)	1 (7.1)
Logistic regression and support vector machines	1 (7.1)
Logistic regression and neural networks	1 (7.1)
Relevant model performance measures evaluated for addressing prediction models	
AUC, P value of Hosmer-Lemeshow test	5 (35.7)
AUC	4 (28.6)
AUC, sensitivity, specificity	2 (14.3)
P value of Hosmer-Lemeshow test	1 (7.1)
Expected and observed	1 (7.1)
Sensitivity, specificity	1 (7.1)
Develop prediction models (n=11)	
Statistical method for selecting predictors during addressing prediction models	
Univariate analysis of predictors by P value	3 (27.3)
Univariate analysis of predictors by P value and other specific predictors	3 (27.3)
Stepwise selection	2 (18.1)
Not reported	3 (27.3)
Handling the predictors for addressing prediction models	
Continuous predictor was transformed into categories	4 (36.4)
Not reported	7 (63.6)

EMR: electronic medical records

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Risk of bias assessment

The risk of bias for 14 prediction models in the domains of participants, predictors, and outcome was low for most studies, while the risk of bias in the domain of sample size and missing data and statistical analysis was generally high (Table 4). Studies rated high and unclear risk of bias in the domains of sample size and missing data, due to low number of outcomes per variable (EPV < 10), or lack of information about the method on handling missing data. The main reasons for studies rated high and unclear risk of bias in the domains of statistical analysis were as below: the predictors are selected on the basis of univariable analysis prior to multivariable modeling, lack of information on whether continuous predictors are examined for nonlinearity and how categorical predictor groups are defined, and either calibration or discrimination are not reported.

Table 4. Risk of bias of included prediction model studies

Study ID	Participants	predictors	Outcome	Sample size and missing data	Statistical analysis
Zhang et al (2015)[34]	L	L	L	H	H
Tolenaar et al (2014)[8]	L	L	L	H	H
Mehta et al (2002)[7]	L	L	L	U	U
Ghoreishi et al (2018)[35]	L	L	H	U	H
Centofanti et al (2006)[36]	L	L	L	U	H
Santini et al (2007)[37]	L	L	L	U	H
Rampoldi et al (2007)[38]	L	L	L	L	H
Leontyev et al (2016)[39]	L	L	L	U	H
Zhang et al (2019)[40]	L	L	L	H	H
Macrina et al (2010)[41]	L	L	L	H	H
Macrina et al (2009)[42]	L	L	L	H	H
Ge et al (2013)[43]	H	H	L	H	H
Yu et al (2016)[44]	L	L	L	H	H
Vrsalovic et al (2015)[9]	L	L	L	H	H

L: low risk; H: high risk; U: unclear risk

Discussion

Summary study findings

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In this systematic review, we identified 32 studies addressing prognostic factors or prediction models for mortality among AAD patients. As noticed in this review, the performance of prognostic factors or prediction models was most commonly evaluated by the AUC and H-L test. Most assessment of prognostic factors demonstrated moderate discrimination. The factors using combined TNC and D-dimer, or combined D-dimer and CRP showed strong discrimination (AUC 0.95). The prediction models showed poor to strong discrimination (AUC 0.49 to 0.91). The prediction model EuroSCORE II showed poor discriminative ability (AUC 0.49) and poor calibration (P value for the H-L test. <0.001). One explanation may be that EuroSCORE II is a risk model which allows the calculation of the risk of death after a heart surgery, and is not related to prognosis of patients with AAD, because not all patients with aortic dissection undergo surgical treatment, and some of them undergo endovascular treatment. Mehta et al.[7] model showed better discrimination (0.74) than the EuroSCORE II. Meanwhile, Mehta et al used IRAD from multinational data reported good calibration. Through external validation, IRAD score showed moderate discrimination (AUC 0.74), addition of CRP to IRAD score notably improved discrimination (AUC 0.89). Hence, the prediction model for mortality in AAD should consider including biomarkers as predictors to improve discrimination.

In this systematic review, we found that most studies had small number of sample sizes and events, were derived from a single-center study, and a relatively large proportion of studies chose to use retrospective data. Most studies did not describe information on missing data nor accounted for appropriate statistical methods for handle missing data.

For developing or validating prediction models, we found that most were considered at high risk of bias; the number of EPV in most studies was relatively small, which result in prediction performance of models being possibly biased;[45 46] most studies did not evaluate both discrimination and calibration. Almost all studies reported discriminative ability of prediction models, while only six studies reported calibration. For developing prediction models, we found that some studies based on statistical significance for

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selecting variable may lead to suboptimal models; most studies did not report how to handle the continuous variable, and linear assumption may be inappropriate.

Implications for future study

Although some studies showed good discrimination and calibration. Our findings highlighted important methodological limitations among those studies. Then it is possible that the result is not accurate and reliable. So in the future, studies about prognostic factors or prediction models for mortality in AAD should enroll large patient population from multicenter setting, meanwhile consider cohort designs, the imputation of missing data. Multiple imputation techniques to deal with missing data are important when evaluating model performance. Excluding cases with missing data may lead to biased results.[47]

Studies about prediction models for mortality in AAD should consider appropriate methods for selecting variable and handling the continuous variable, and evaluating both discrimination and calibration. The number of participants and events should be planned, and the number of EPV should be at least 10. If the number of events is low relative to the number of predictors, penalized regression may be better than the standard regression. Stability selection and subsampling have demonstrated to yield more stable models based on a consistent selection of variables, so they should be used in future studies for prediction model.[48] Discrimination should not be reported in isolation because a poorly calibrated model can present the same discriminative capacity as a perfectly calibrated one.[49] Reporting both discrimination and calibration is highly recommended for evaluating performance measures. Validating the predictions models should be considered, as both model development and validation are essential processes for establishing a useful prediction model.[50]

A prediction model most suitable for clinical practice should include a relatively small number of variables, be easily interpreted, and have good statistical performance. Apart

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from the well-established IRAD model, our review found that the combined IRAD score and CRP model used less variables and showed better discrimination than IRAD score alone. These characteristics may warrant daily practice of the combine model. Moreover, future studies may consider updating IRAD model by including other relevant biomarkers, which may further improve prognostic performance in clinical practice.

Strengths and limitations

To our knowledge, no systematic review looking at the methodology characteristics and performance of prognostic factors or predictive models for mortality in AAD has been published. Whether these existing prognostic factors or prediction models may be used to guide or improve clinical practice remains underexplored. Should we seek better prognostic factors or prediction models? Should we continue using and validating these prognostic factors or prediction models? There is consensus on this issue among commentators. We should seek better prognostic factors or prediction models. Substantial efforts are warranted to strengthen the use of rigorous methods for the accuracy and reliability of the performance in the future research.

A limitation of the present study is that our review about the methodological characteristics was primarily based on reporting. There might be cases that the researchers had considered the methodological issues but did not clearly report. This situation also emphasized the importance of complete reporting.

Conclusions

In conclusion, D-dimer, NLR, and CRP predictors were the most commonly used biomarkers, the performance of prognostic factors showed a poor to strong discrimination, the prediction models varied substantially, only six studies reported the calibration, and of which five reported good calibration. Meanwhile, many of these prognostic factors or predictive models are weak methodologically, several important

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issues are needed to consider for strengthening for predicting mortality in AAD, such as the sample size, the methods for handling missing data, appropriate statistical analysis methods, and reporting both calibration and discrimination for prediction models. Substantial efforts are warranted to improve the use of the methods for better care of this population.

Contributors

Study concept and design: Yan Ren. Screening the articles: Yan Ren and Shiyao Huang. Acquisition of data: Yan Ren, Shiyao Huang and Chunrong Liu. Analysis of data: Yan Ren and Shiyao Huang. Drafting of the manuscript: Yan Ren. Writing - review & editing: Qianrui Li, Ling Li, Jing Tan, Kang Zou, and Xin Sun. Study supervision: Xin Sun.

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Competing Interests

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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All data relevant to the study are included in the article or uploaded as supplementary information. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Ethics approval

The current study is a secondary analysis of the research data. No ethical approval was required for our study.

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Figure 1. Flow chart of study selection

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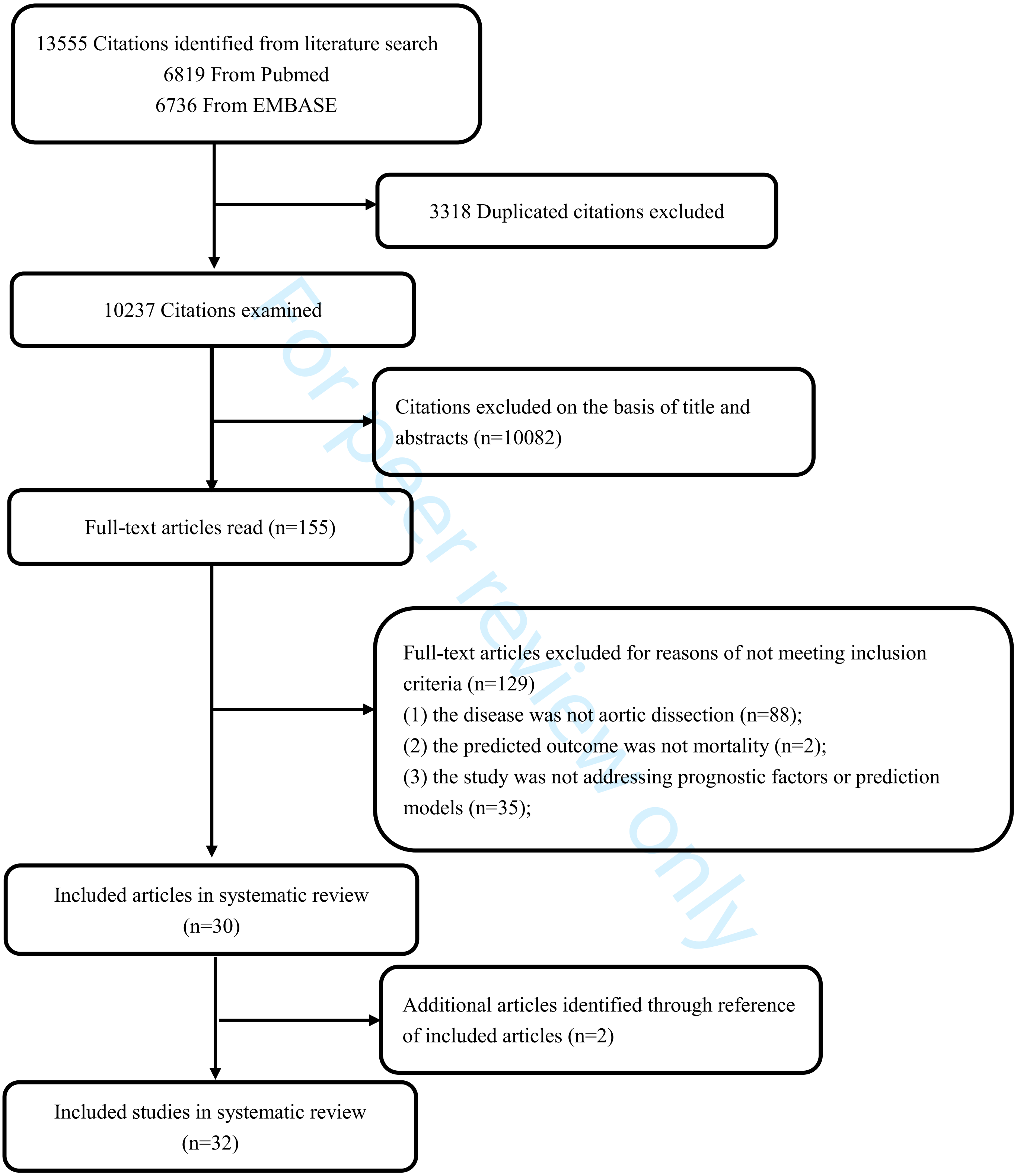

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Appendix Table 1. General characteristics of studies included in the systematic review

Study ID	Region	Period of Data Collection	Centers (n)	Sample size for analysis (n)	Event	Study design	Data sources	Age (Mean±SD or median (interquartile range)) (years)	Male (%)	Study purpose
Liu et al (2018a)	China	2006.01-2017.01	1	143	32	Retrospective cohort	EMR data	5[illegible].0 (4[illegible].0, 62.0)	72.00%	Prediction performance of prognostic factors
Zindovic et al (2018)	Sweden	2005.01-2017.02	1	277	37	Retrospective cohort	EMR data	[illegible]3.[illegible]±11.4	63.86%	Prediction performance of prognostic factors
Oz et al (2017)	Turkey		1	57	15	Retrospective cohort	EMR data	[illegible]4.[illegible]±10.5	15.80%	Prediction performance of prognostic factors
Li et al (2016)	China	2010.05-2014.06	4	103	36	Prospective cohort	EMR data	54.[illegible]±13.4	68.93%	Prediction performance of prognostic factors
Vrsalovic et al (2015)	Croatia	2006.01-2013.12	1	54	24	Retrospective cohort	EMR data	69.[illegible]±14.0	63.00%	External validation
Karakoyun et al (2015)	Turkey	2009-2013	1	35	9	Retrospective cohort	EMR data	55.[illegible]±7.95	80.00%	Prediction performance of prognostic factors
Wen et al (2019)	China	2008.03-2012.01	1	122	29	Prospective cohort	Cohort	50.[illegible]±8.35	84.43%	Prediction performance of prognostic factors
Liu et al (2018b)	China	2012.12-2016.06	1	192	19	Retrospective cohort	EMR data	[illegible].0 (4[illegible].0, 62.0)	78.60%	Prediction performance of prognostic factors
Bennett et al (2017)	USA	2000-2014	1	144	38	Retrospective cohort	EMR data	58.7 (4[illegible].9, 69.7)	67.00%	Prediction performance of prognostic factors
Zhang et al (2015)	China	2008.01-2013.10	1	360	77	Prospective cohort	Cohort	57.[illegible]±12.6	75.80%	Develop a model without validation

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LAFÇI et al (2014)	Turkey	2007.01-2012.01	1	104	33		Retrospective cohort	EMR data	55.[illegible]±14.0	73.08%	Prediction performance of prognostic factors
Wen et al (2013)	China	2007.01-2011.10	1	114	31		Prospective cohort	Cohort	48.8±7.6	84.20%	Prediction performance of prognostic factors
Guo et al (2019)	China	2015.12-2017.08	1	109	31		Prospective cohort	Cohort	[illegible]2.[illegible]±12.3	59.63%	Prediction performance of prognostic factors
Ohlmann et al (2006)	France	1997.01-2003.12	1	93	22		Retrospective cohort	EMR data	[illegible]3.[illegible]±12.6	66.00%	Prediction performance of prognostic factors
Ge et al (2013)	China	2009.02-2012.02	1	384	31		Retrospective cohort	Cohort	[illegible]±10.8	20.05%	External Validation
Tolenaar et al (2014)	Multinational	1996.01-2013.04	Multicenter	1034	110		Prospective cohort	Registry	63.5±14.0	65.10%	Develop a model without validation
Mehta et al (2002)	6 countries	1996.01-1999.12	18	547	178		Prospective cohort	Registry	61.[illegible]±14.1	65.50%	Develop a model without validation
Yu et al (2016)	USA	2008-2013	1	79	13		Retrospective cohort	EMR data	60(interquartile range: 51-70)	65.80%	External validation
Feng et al (2017)	China	2010.02-2014.12	1	136	39		Prospective cohort	EMR data	53.7±10.3	56.60%	Prediction performance of prognostic factors
Ghoreishi et al (2018)	USA	2002.01-2015.12	1	269		43	Retrospective cohort	EMR data	5[illegible]±14	67.00%	Develop a model without validation
Zhang et al (2016)	China	2014.01-2015.06	1	67		26	Retrospective cohort	EMR data			Prediction performance of prognostic factors
Macrina et al (2010)	Italy	2002.01-late 2008	2	235		84	Prospective cohort	EMR data			Develop a model with internal validation
Macrina et al (2009)	Italy	2001.01-early 2008	2	208		53	Prospective cohort	EMR data	Survivors:61±12; Nonsurvivors: 6[illegible]±10	64.00%	Develop a model with internal validation

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Li et al (2019)	China	2007-2013.08	1	134	19	Prospective cohort	EMR data	Men: 50.59 ± 13.70, Women: 52.17 ± 1[illegible].55	67.3%	Prediction performance of prognostic factors
Centofanti et al (2006)	Multinational	1980-2004	Multicenter	616	154	Prospective cohort	Registry			Develop a model without validation
Santini et al (2007)		1979-2004		311	72	Retrospective cohort	EMR data	[illegible]9.5 ± 13	72.00%	Develop a model without validation
Rampoldi et al (2007)	Multinational	1996-2003	18	682	163	Retrospective cohort	Registry	5[illegible].9 ± 13.8	70.30%	Develop a model without validation
Leontyev et al (2016)	Multinational	1996-2011	2	534	100	Prospective cohort	Registry	61 ± 14	63.70%	Develop a model without validation
Zhang et al (2019)	China	2013.11.01-2016.10.30	1	188	17	Prospective cohort	EMR data	57.7 ± 12.6	77.10%	Develop a model without validation
Zhang et al (2020)	China	2016.01-2019.06	1	186	40	Retrospective cohort	EMR data	50 ± 12	80.00%	Prediction performance of prognostic factors
Bedel et al (2019)	Finland	2013.01-2018.06	1	96	17	Retrospective cohort	EMR data	63.7±13.4	81.20%	Prediction performance of prognostic factors
Gong et al (2019)	China	2015.01-2017.05	1	583	70	Retrospective cohort	EMR data	48.05 ± 11.29		Prediction performance of prognostic factors

NLR: neutrophil lymphocyte ratio; hs-TnT: high-sensitivity cardiac troponin T; hs-CRP: high-sensitivity C-reactive protein; IRAD score: international registry of acute aortic dissection score; CRP: C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; BUN: blood urea nitrogen; TNC: Tenascin-C; EuroSCORE II: European System for Cardiac Operative Risk Evaluation.

Notes: The Liu et al (2018a) study and the Liu et al (2018b) study are the different prognostic models. Liu et al (2018a) study is for the relationship between fibrinogen and in-hospital mortality in patients with type A acute aortic dissection. Liu et al (2018b) study is for the relationship between blood urea nitrogen and in-hospital mortality of patients with acute aortic dissection.

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Appendix A Search strategies

Database: PubMed (until June, 2020)
#1 (aortic dissecting aneurysm[MeSH Terms]) OR aortic dissecting aneurysm #2 (aortic aneurysm[MeSH Terms]) OR aortic aneurysm #3 (aortic dissection*[MeSH Terms]) OR aortic dissection* #4 (aortic dissecting hematoma) OR aortic dissecting hematoma[MeSH Terms] #5 #1 OR #2 OR #3 OR #4 #6 (validat* OR predict*[tiab] OR rule*) OR (predict* AND (outcome* OR risk* OR model*)) OR ((history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor*) AND (predict* OR model* OR decision* OR identif* OR prognos*)) OR (decision* AND (model* OR clinical* OR logistic models)) OR (prognostic AND (history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor* OR model*)) OR "stratification" OR "ROC Curve"[MeSH] OR "discrimination" OR "discriminate" OR "c statistic" OR "area under the curve" OR "AUC" OR "Calibration" OR "Indices" OR "algorithm" OR "Multivariable") #7 ((cohort[MeSH Terms]) OR cohort) OR (observational[MeSH Terms]) OR observational) OR ((prospective[MeSH Terms]) OR prospective) OR((trial[MeSH Terms]) OR trial) OR ((epidemiology[MeSH Terms]) OR epidemiology) OR ((longitudinal[MeSH Terms]) OR longitudinal) #8 #5 AND #6 AND #7 #9 (Animals[MeSH] NOT Humans[MeSH]) #10 #8 NOT #9 #11 English[Language] #12 #10 AND #11
Database: EMBASE (until June, 2020)
#1 aortic dissecting aneurysm.mp. or exp dissecting aortic aneurysm/ #2 aortic aneurysm.mp. or exp aortic aneurysm/ #3 aortic dissection$.mp. or exp aortic dissection/ #4 exp aortic dissection/ or aortic dissecting hematoma.mp. #5 #1 or #2 or #3 or #4 #6 exp cohort analysis/ or cohort.mp. #7 exp observational study/ or observational.mp. #8 prospective.mp. or exp prospective study/ #9 exp controlled clinical trial/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or trial.mp. or exp pragmatic trial/ or exp "controlled clinical trial (topic)"/ or exp clinical trial/ or exp adaptive clinical trial/ or exp randomized controlled trial/ #10 exp epidemiology/ or epidemiology.mp. #11 exp longitudinal study/ or longitudinal.mp. #12 #6 or #7 or #8 or #9 or #10 #13 (validat* or predict* or rule* or (predict* and (outcome* or risk* or model*)) or ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)) or (decision* and (model* or clinical* or logistic models)) or (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)) or ('stratification' or 'ROC Curve' or 'discrimination' or 'discriminate' or 'c statistic' or 'area under the curve' or 'AUC' or 'Calibration' or 'Indices' or 'algorithm' or 'Multivariable')).af.

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#14	#5 and #12 and #13
#15	limit #14 to (human and english language)

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Appendix B

The questionnaire for prognostic factors and prediction models in acute aortic dissection

1. Study basic information

1.1 First author	
1.2 Year of Publication	
1.3 Region	
1.4 Period of Data Collection	
1.5 Dissection type	1) A 2) B 3) A/B
1.6 Outcome (such as in-hospital mortality、one-year mortality)	
1.7 age(SD)(years)	
1.8 male(%)	
1.9 Study purpose	1) Prediction performance of prognostic factors 2) Develop a model without validation 3) External validation

2. performance information of prognostic factors or prediction models

2.1 Prognostic factors	
2.1.1 predictors 1	
The name of the predictors	
Cut-off value(or score)	
AUC(95% CI)	
P value of Hosmer-Lemeshow test	
sensitivity	
specificity	
2.1.2 predictors 2	
The name of the predictors	
Cut-off value(or score)	
AUC(95% CI)	
P value of Hosmer-Lemeshow test	
sensitivity	
specificity	
2.1.3 predictors 3	
The name of the predictors	
Cut-off value(or score)	
AUC(95% CI)	
P value of Hosmer-Lemeshow test	
sensitivity	

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specificity	
……	
2.2 Prediction models	
2.2.1 Number of predictors in model, please specify the name of the predictors.	
2.2.2 the type of model Check all that apply	1) derivation model 2) internal validation 3) external validation
2.2.2.1 Sampling method used for internal validation Check all that apply	1) Bootstrapping 2) Cross validation 3) Split-sample 4) Jackknifing procedure 5) Leave-one-out method 6) Monte Carlo simulations Other, specify
2.2.2.2 External validation Check all that apply	1) Temporal validation 2) Geographical validation 3) Other, specify
2.2.3 What was the method used for assess the overall performance Check all that apply	1) R^2 2) Nagelkerke's R^2 3) Brier Score 4) Other, specify
2.2.3.1 The reported value of the overall performance	
2.2.4 What was the method used for assessing discrimination Check all that apply	1) C statistic (ROC curve) 2) Harrell's overall c statistic 3) Discrimination Slope(Box plots) 4) Lorenz curve 5) Log-rank 6) Other, specify
2.2.4.1 The reported value of discrimination	
2.2.5 What was the method used for assessing calibration Check all that apply	1) P value of Hosmer-Lemeshow test 2) Calibration plot 3) Calibration slope 4) Other, specify
2.2.5.1 The reported value or judge of calibration	
2.2.6 Reclassification NRI, % (95% CI/P Value)(NRI, Net reclassification Index)	
2.2.7 Reclassification IDI, % (95% CI/P Value)(IDI, Integrative Discriminative Index)	

3. The questionnaire about the methodological characteristics consists of five domains

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Domain 1: Study design

1.1 No. of Centers	
1.2 No. of patients	
1.3 No. of Events	
1.4 Source of data (e.g., cohort, case-control, randomized trial participants, EMR or registry data)	
1.5 Study design (Retrospective cohort、Prospective cohort、Nested case-control、Case-control study)	

Domain 2: Participants

2.1 Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data	1) Yes, specify 2) No, specify 3) Not reported
2.2 Whether did the study clearly describe inclusion criteria	1) yes 2) no 3) Not reported
2.3 Whether did the study clearly describe exclusion criteria	1) yes 2) no 3) Not reported

Domain 3: Predictors

3.1 Consistent definition/diagnostic criteria of predictors used in all participants	1) Yes 2) No 3) Not reported
3.2 Consistent measurement of predictors used in all participants	1) Yes 2) No 3) Not reported

Domain 4: Outcome

4.1 Consistent definition/diagnostic criteria of outcomes used in all participants	1) Yes 2) No 3) Not reported
4.2 Consistent measurement of outcomes used in all participants	1) Yes 2) No 3) Not reported

Domain 5: Analysis

5.1 Were all enrolled participants included in the analysis?	1) yes 2) no

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	3) Not reported
5.2 Number of outcomes/events in relation to the number of predictors in multivariable analysis (Events Per Variable: EPVs)	1) ≥20 2) 10-20 3) <10
5.3 Statistical method for selecting predictors during addressing prognostic factors or prediction models Check all that apply	1) Backward selection 2) Forward selection 3) Added a specific predictor for existing model 4) All predictors included regardless of statistical significance 5) Univariate analysis of predictors by p value 6) Other, specify: 7) Not reported
5.4 Handling the predictors for addressing prognostic factors or prediction models Check all that apply	1) Continuous predictor was transformed into categories 2) Non-linear transformation 3) Not reported 4) Other, specify
5.5 Were missing outcome data reported, and the methods handling missing outcome	1) Yes, specify 2) No 3) Not reported
5.6 Was any missing predictor data reported, and the methods handling missing predictor	1) Yes, specify 2) No 3) Not reported
5.7 Model structure used in the study	1) Linear regression 2) Logistic regression 3) Multinomial logistic 4) Cox regression 5) Decision tree 6) Bayesian (and logistic) 7) Machine learning 8) Artificial neural network 9) Partial least squares-discriminant analysis 10) Other, specify
5.8 Were relevant model performance measures evaluated for addressing prognostic factors or prediction models Check all that apply	1) Both calibration and discrimination are evaluated 2) Only calibration is evaluated 3) Only discrimination is evaluated 4) Other, specify

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Appendix C Risk of bias assessment

Domain 1: Participants

1.1 Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If a cohort design (including RCT or proper registry data) or a nested case–control or case–cohort design (with proper adjustment of the baseline risk/hazard in the analysis) has
been used.

No/probably no: If a nonnested case–control design has been used.

No information: If the method of participant sampling is unclear.

1.2 Were all inclusions and exclusions of participants appropriate? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If inclusion and exclusion of participants was appropriate, so participants correspond to unselected participants of interest.

No/probably no: If participants are included who would already have been identified as having the outcome and so are no longer participants at suspicion of disease (diagnostic studies) or at risk of developing outcome (prognostic studies), or if specific subgroups are excluded that may have altered the performance of the prediction model for the intended target population.

No information: When there is no information on whether inappropriate inclusions or exclusions took place. Risk of bias introduced by participants or data sources

Risk of bias introduced by predictors or their assessment（Low、High、Unclear）

Low risk of bias: If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.

High risk of bias: If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.

Unclear risk of bias: If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 2: Predictors

2.1 Were predictors defined and assessed in a similar way for all participants? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If definitions of predictors and their assessment were similar for all participants.

No/probably no: If different definitions were used for the same predictor or if predictors requiring subjective interpretation were assessed by differently experienced assessors.

No information: If there is no information on how predictors were defined or assessed.

2.2 Were predictor assessments made without knowledge of outcome data? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If outcome information was stated as not used during predictor assessment or was clearly not (yet) available to those assessing predictors.

No/probably no: If it is clear that outcome information was used when assessing predictors.

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No information: No information on whether predictors were assessed without knowledge of outcome information.

2.3 Are all predictors available at the time the model is intended to be used? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: All included predictors would be available at the time the model is intended to be used for prediction.

No/probably no: Predictors would not be available at the time the model is intended to be used for prediction.

No information: No information on whether predictors would be available at the time the model is intended to be used for prediction.

Risk of bias introduced by predictors or their assessment（Low、High、Unclear）

Low risk of bias: If the answer to all signaling questions is "Yes" or "Probably Yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low, e.g., use of objective predictors not requiring subjective interpretation.

High risk of bias: If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias.

Unclear risk of bias: If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put the domain at high risk of bias.

Domain 3: Outcome

3.1 Was the outcome determined appropriately? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If a method of outcome determination has been used which is considered optimal or acceptable by guidelines or previous publications on the topic. Note: This is about level of measurement error within the method of determining the outcome (see concerns for applicability about whether the *definition* of the outcome method is appropriate).

No/probably no: If a clearly suboptimal method has been used that causes unacceptable error in determining outcome status in participants.

No information: No information on how outcome was determined.

3.2 Was a prespecified or standard outcome definition used? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If the method of outcome determination is objective, *or* if a standard outcome definition is used, *or* if prespecified categories are used to group outcomes.

No/probably no: If the outcome definition was not standard and not prespecified.

No information: No information on whether the outcome definition was prespecified or standard.

3.3 Were predictors excluded from the outcome definition? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If none of the predictors are included in the outcome definition.

No/probably no: If ≥1 of the predictors forms part of the outcome definition.

No information: No information on whether predictors are excluded from the outcome definition.

3.4 Was the outcome defined and determined in a similar way for all participants? (Yes/probably yes、No/probably no、No information)

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Yes/probably yes: If outcomes were defined and determined in a similar way for all participants.

No/probably no: If outcomes were clearly defined and determined in a different way for some participants.

No information: No information on whether outcomes were defined or determined in a similar way for all participants.

3.5 Was the outcome determined without knowledge of predictor information? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If predictor information was not known when determining the outcome status, *or* outcome status determination is clearly reported as determined without knowledge of predictor information.

No/probably no: If it is clear that predictor information was used when determining the outcome status.

No information: No information on whether outcome was determined without knowledge of predictor information.

3.6 Was the time interval between predictor assessment and outcome determination appropriate? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If the time interval between predictor assessment and outcome determination was appropriate to enable the correct type and representative number of relevant outcomes to be recorded, *or* if no information on the time interval is required to allow a representative number of the relevant outcome occur or if predictor assessment and outcome determination were from information taken within an appropriate time interval.

No/probably no: If the time interval between predictor assessment and outcome determination is too short or too long to enable the correct type and representative number of relevant outcomes to be recorded.

No information: If no information was provided on the time interval between predictor assessment and outcome determination.

Risk of bias introduced by predictors or their assessment（Low、High、Unclear）

Low risk of bias: If the answer to all signaling questions is “Yes” or “Probably yes,” then risk of bias can be considered low. If ≥1 of the answers is “No” or “Probably no,” the judgment could still be low risk of bias, but specific reasons should be provided why the risk of bias can be considered low, e.g., when the outcome was determined with knowledge of predictor information but the outcome assessment did not require much interpretation by the assessor (e.g., death regardless of cause).

High risk of bias: If the answer to any of the signaling questions is “No” or “Probably no,” there is a potential for bias.

Unclear risk of bias: If relevant information about the outcome is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 4: Sample size and missing data

4.1 Were there a reasonable number of participants with the outcome? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is ≥20 (EPV ≥20 Number of outcomes/events

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in relation to the number of candidate predictors (Events Per Variable: For EPVs between 10 and 20, the item should be rated as either probably yes or probably no, depending on the outcome frequency, overall model performance, and distribution of the predictors in the model.)). For model validation studies, if the number of participants with the outcome is ≥100.

No/probably no: For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is <10 (EPV <10). For model validation studies, if the number of participants with the outcome is <100.

No information: For model development studies, no information on the number of candidate predictor parameters or number of participants with the outcome, such that the EPV cannot be calculated. For model validation studies, no information on the number of participants with the outcome.

4.2 Were all enrolled participants included in the analysis? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If all participants enrolled in the study are included in the data analysis.

No/probably no: If some or a subgroup of participants are inappropriately excluded from the analysis.

No information: No information on whether all enrolled participants are included in the analysis.

4.3 Were participants with missing data handled appropriately? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If there are no missing values of predictors or outcomes and the study explicitly reports that participants are not excluded on the basis of missing data, or if missing values are handled using multiple imputation. Handling of missing data (e.g., complete-case analysis, imputation, or other methods)

No/probably no: If participants with missing data are omitted from the analysis, or if the method of handling missing data is clearly flawed, e.g., missing indicator method or inappropriate use of last value carried forward, or if the study had no explicit mention of methods to handle missing data.

No information: If there is insufficient information to determine if the method of handling missing data is appropriate.

Risk of bias introduced by predictors or their assessment（Low、High、Unclear）

Low risk of bias: If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.

High risk of bias: If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.

Unclear risk of bias: If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 5: Statistical analysis

5.1 Were continuous and categorical predictors handled appropriately? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If continuous predictors are not converted into ≥2 categories when included in the model (i.e., dichotomized or categorized), or if continuous predictors are examined for

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nonlinearity using, for example, fractional polynomials or restricted cubic splines, or if categorical predictor groups are defined using a prespecified method. For model validation studies, if continuous predictors are included using the same definitions or transformations, and categorical variables are categorized using the same cut points, as compared with the development study.

No/probably no: If categorical predictor group definitions do not use a prespecified method. For model development studies, if continuous predictors are converted into ≥2 categories when included in the model. For model validation studies, if continuous predictors are included using different definitions or transformations, or categorical variables are categorized using different cut points, as compared with the development study.

No information: No information on whether continuous predictors are examined for nonlinearity and no information on how categorical predictor groups are defined. For model validation studies, no information on whether the same definitions or transformations and the same cut points are used, as compared with the development study.

5.2 Was selection of predictors based on univariable analysis avoided?† (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If the predictors are not selected on the basis of univariable analysis prior to multivariable modeling.

No/probably no: If the predictors are selected on the basis of univariable analysis prior to multivariable modeling.

No information: If there is no information to indicate that univariable selection is avoided.

5.3 Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If any complexities in the data are accounted for appropriately, or if it is clear that any potential data complexities have been identified appropriately as unimportant.

No/probably no: If complexities in the data that could affect model performance are ignored.

No information: No information is provided on whether complexities in the data are present or accounted for appropriately if present.

5.4 Were relevant model performance measures evaluated appropriately? (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If both calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and discrimination (C-statistic, D-statistic, log-rank) are evaluated appropriately with confidence intervals (including relevant measures tailored for models predicting survival outcomes). Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used.

No/probably no: If both calibration and discrimination are not evaluated, or if only goodness-of-fit tests, such as the Hosmer–Lemeshow test, are used to evaluate calibration, or if for models predicting survival outcomes performance measures accounting for censoring are not used, or if classification measures (like sensitivity, specificity, or predictive values) were presented using predicted probability thresholds derived from the data set at hand.

No information: Either calibration or discrimination are not reported, or no information is provided as to whether appropriate performance measures for survival outcomes are used (e.g., references to relevant literature or specific mention of methods, such as using Kaplan–Meier estimates), or no information on thresholds for estimating classification measures is given.

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5.5 Were model overfitting and optimism in model performance accounted for?† (Yes/probably yes、No/probably no、No information)

Yes/probably yes: If internal validation techniques, such as bootstrapping and cross-validation including all model development procedures, have been used to account for any optimism in model fitting, and subsequent adjustment of the model performance estimates have been applied.

No/probably no: If no internal validation has been performed, or if internal validation consists only of a single random split-sample of participant data, or if the bootstrapping or cross-validation did not include all model development procedures including any variable selection.

No information: No information is provided on whether internal validation techniques, including all model development procedures, have been applied.

5.6 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?†(Yes/probably yes、No/probably no、No information)

Yes/probably yes: If the predictors and regression coefficients in the final model correspond to reported results from multivariable analysis.

No/probably no: If the predictors and regression coefficients in the final model do not correspond to reported results from multivariable analysis.

No information: If it is unclear whether the regression coefficients in the final model correspond to reported results from multivariable analysis.

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Risk of bias introduced by the analysis（Low、High、Unclear）

Low risk of bias: If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be low risk of bias, but specific reasons should be provided why the risk of bias can be considered low.

High risk of bias: If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias.

Unclear risk of bias: If relevant information about the analysis is missing for some of the signaling questions but none of the signaling question answers is judged to put the analysis at high risk of bias.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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