New Guideline for the Reporting of Studies Developing, Validating, or Updating a Multivariable Clinical Prediction Model: The TRIPOD Statement

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Abstract: Prediction models are developed to aid health care providers in estimating the probability that a specific outcome or disease is present (diagnostic prediction models) or will occur in the future (prognostic prediction models), to inform their decision making. Prognostic models here also include models to predict treatment outcomes or responses; in the cancer literature often referred to as predictive models. Clinical prediction models have become abundant. Pathology measurement or results are frequently included as predictors in such prediction models, certainly in the cancer domain. Only when full information on all aspects of a prediction modeling study are clearly reported, risk of bias and potential usefulness of the prediction model can be adequately assessed. Many reviews have illustrated that the quality of reports on the development, validation, and/or adjusting (updating) of prediction models, is very poor. Hence, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative has developed a comprehensive and user-friendly checklist for the reporting of studies on, both diagnostic and prognostic, prediction models. The TRIPOD Statement intends to improve the transparency and completeness of reporting of studies that report solely on development, both development and validation, and solely on the validation (with or without updating) of diagnostic or prognostic, including predictive, models.

Key Words: prediction, prediction model, prognostic model, predictive model, diagnostic model, reporting, transparency

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In medicine, patients and their care providers are confronted with making numerous decisions that are commonly, if not always, made on the basis of a probability; a probability that a specific disease or condition is present (diagnostic setting) or a specific event or outcome will occur in the future (prognostic setting). Such probability estimates are frequently, in many clinical domains, based on pathology measurements or results as well. In the diagnostic setting, the probability that a particular disease is present is used, for example, to inform the referral of patients for further testing, initiate treatment directly, or reassure patients that a serious cause for their complaint is unlikely. In the prognostic setting, predictions are used for planning lifestyle or therapeutic decisions based on the probability of developing a particular outcome, health state, or therapeutic effect, within a specific time period. Prognostication thus also includes prediction of treatment outcomes or responses. This time period may range from hours (eg, predicting postoperative complications) to weeks or months (eg, predicting 30-d mortality after brain surgery), or years (predicting the 5-y risk of surviving colon carcinoma). Moreover, prognostic probabilities can be estimated from ill or healthy individuals; they simply refer to the prediction of an outcome in the future in individuals at risk for that outcome.

In practice, diagnostic and prognostic probability estimations are rarely based on a single test result or predictor, and often not even on a single pathologic finding or parameter. A single test result, either from pathology or any other type of testing, is commonly insufficient to provide reliable and accurate estimates on a patient's diagnosis or prognosis. To guide practitioners and patients in these probability estimations, so-called multivariable prediction models are developed. Multivariable prediction models convert multiple (2 or more) pieces of information (called predictors) from the patient into a diagnostic or prognostic probability. In virtually all medical domains, such prediction models are being developed, validated, updated, and implemented with the aim to assist doctors and individuals in estimating risk and potentially influence their, ideally shared, decision making. Pathology measurements or results are frequently included as predictors in prediction models, notably in the cancer field. Other names for a prediction model include risk prediction model, predictive model, prediction index or rule, and risk score. As stated above, the outcome to be predicted by a prognostic model may also include a "treatment response." In the cancer literature, such prognostic models are sometimes referred to as predictive models but are here and in the TRIPOD Statement, covered by the term prognostic models. Predictors are also referred to as covariates, risk indicators, prognostic factors, determinants, test results, or—more statistically—independent variables. They may range from demographics (eg, age and sex), medical history taking, and physical examination results, to results from imaging, electrophysiology, blood and urine measurements, and pathology results, to results from genomics, proteomics, transcriptomics, pharmacogenomics, metabolomics, and other new biological measurement platforms that continuously emerge.

Prediction models, diagnostic and prognostic (including predictive) models, are becoming increasingly abundant in the medical literature, and policymakers are increasingly

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TABLE 1. The TRIPOD Checklist

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted	
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions	
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models	
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both	
Methods				
Source of data	4a	D;V	Describe the study design or source of data (eg, randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable	
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and if applicable, end of follow-up	
Participants	5a	D;V	Specify key elements of the study setting (eg, primary care, secondary care, general population) including number and location of centers	
	5b	D;V	Describe eligibility criteria for participants	
	5c	D;V	Give details of treatments received, if relevant	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted	
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured	
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors	
Sample size	8	D;V	Explain how the study size was arrived at	
Missing data	9	D;V	Describe how missing data were handled (eg, complete-case analysis, single imputation, multiple imputation) with details of any imputation method	
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses	
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation	
	10c	V	For validation, describe how the predictions were calculated	
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models	
	10e	V	Describe any model updating (eg, recalibration) arising from the validation, if done	
Risk groups	11	D;V	Provide details on how risk groups were created, if done	
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors	
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome	
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors, and outcome)	
Model development	14a	D	Specify the number of participants and outcome events in each analysis	
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome	
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (ie, all regression coefficients, and model intercept or baseline survival at a given time point)	
	15b	D	Explain how to use the prediction model	
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model	
Model updating	17	V	If done, report the results from any model updating (ie, model specification, model performance)	
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data)	
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data	
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence	
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research	
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study	

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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recommending their use in clinical practice guidelines. In virtually all medical domains, prediction models are being developed, evaluated (validated), and implemented. For some specific diseases, there are overwhelming numbers of competing prediction models for the same outcome or target population. For example, there are over 100 prognostic models for predicting outcome after brain trauma, over 100 models for prostate cancer, and over 60 models for breast cancer prognosis. Given this abundance of published prediction models across almost all clinical domains, critical appraisal and synthesis of the available reports is a requirement to enable readers, care providers, and policymakers to judge which models are useful in which situations. Such an assessment, in turn, is possible only if key details of how prediction models were developed and validated are clearly reported. Only with full and transparent reporting of information on all aspects of a prediction model development, validation or updating, can generalizability and risk of bias of published prediction models be adequately assessed, and subsequent researchers can replicate on the same data, if needed, the steps taken to obtain the same results. However, the overwhelming evidence shows that the quality of reporting of prediction model studies is poor.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative, which has included clinicians, statisticians, epidemiologists, and journal editors, has produced a guideline for the reporting of studies developing, validating, or updating (extending) a prediction model, whether for diagnostic or prognostic purposes.[1] TRIPOD primarily addresses prediction models for binary (eg, disease presence or absence) or time-to-event outcomes (eg, 1-y disease-free-survival), as these are the most common types of outcomes to be predicted in medicine. However, outcomes may also be continuous measurements (eg, blood pressure; tumor size; percentage vessel stenosis; IQ scores; quality of life; length of hospital stay), nominal outcomes (eg, the differential diagnosis rather than target disease present or absent; type of infection defined as viral, bacterial, or no infection), or ordinal outcomes (eg, cancer stage, Glasgow Coma Scale, Rankin scale), for which prediction models may also be developed. Most recommendations and reporting items contained within TRIPOD apply equally to the reporting of studies aimed at developing or validating prediction models for such outcomes. Finally, TRIPOD focuses on prediction or predictive models developed by regression modeling, as this is the approach by which most prediction models are developed, validated, or updated in medical research. However, most items equally apply to prediction tools developed, validated, or updated with other techniques such as classification trees, neural networks, genetic programming, random forests, or vector machine learning techniques. The main difference in these other approaches over regression modeling is the method of data analysis to derive the prediction model. Problems of transparency in these nonregression modeling approaches are a particular concern, especially regarding reproducible research and implementation in practice.

The TRIPOD Statement is a checklist of 22 items (Table 1), deemed essential for transparent reporting of any prediction model study, regardless of the study methods used. The TRIPOD Statement is accompanied by an Explanation and Elaboration article[2] that describes the rationale for the checklist, clarifies the meaning of each item, and discusses why transparent reporting is important, with a view to assessing risk of bias and clinical usefulness of a prediction model. Each item of the TRIPOD checklist is explained in detail and accompanied by published examples of good reporting, of both development and validation of prediction models (as relevant), and often for both diagnosis and prognosis; they illustrate the type of information that is appropriate to report. The Explanation and Elaboration document also provides a valuable reference of issues to consider when designing, conducting, and analyzing prediction model studies.

The endorsement and use of this checklist by researchers and medical journal editors will help ensure that medical research findings are complete and accurately reported, understood by readers, and ultimately used by medical practitioners. The TRIPOD checklist is downloadable via the Web site (http://www.tripod-statement.org). Announcements and information relating to TRIPOD will also be broadcast on the TRIPOD twitter address (@TRIPODStatement). The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (http://www.equator-network.org) will help disseminate and promote the TRIPOD Statement.

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