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ORIGINAL ARTICLE

The use of rigorous methods was strongly warranted among prognostic prediction models for obstetric care

Jing Tan[a], Yana Qi[a], Chunrong Liu[a], Yiquan Xiong[a], Qiao He[a], Guiting Zhang[a], Meng Chen[b], Guolin He[b], Wen Wang[a], Xinghui Liu[b], Xin Sun[a,*]

[a]*Chinese Evidence-based Medicine Center and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China*

[b]*Department of Obstetrics and Gynecology, and Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China*

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Abstract

Objective: The objective of the study was to examine methodological characteristics about the design and conduct in prognostic prediction models used for obstetric care.

Study Design and Setting: We searched PubMed for studies on prognostic prediction models for obstetric care, published in top general medicine or major specialty journals between January 2011 and February 2018. Teams of method-trained investigators independently screened titles and abstracts and collected data using a prespecified, pilot-tested, structured questionnaire.

Results: In total, 91 studies were eligible, of which two were published in top general medicine journals, 20 (22.0%) involved an epidemiologist or statistician, 18 (19.4%) published study protocols, 53 (58.2%) did not include any model validation, 20 (22.0%) did not clearly state the intended timing of use, 23 (25.3%) had no eligibility criteria, 15 (16.5%) did not use clear criteria for ascertaining outcome, and 69 (75.82%) did not apply blinding to outcome assessment. Among those models, 11 (12.1%) included participants fewer than 200 events, 41 (48.8%) had fewer than 100 events, and 19 (24.7%) had fewer than 10 events per variable.

Conclusion: The prognostic prediction models have important limitations in design and conduct. Substantial efforts are needed to strengthen the production of reliable prognostic prediction models for obstetric care.

Keywords: Prediction model; Prognosis; Obstetric care; Design; Conduct; Methodological survey

1. Introduction

In recent years, prediction models, including prognostic and diagnostic models, have rapidly gained popularity [1−3] and are increasingly used for health care [4,5]. Such models, if validated, may be helpful with assisting health care practitioners in management of diseases, thus improving patient outcomes [4−8]. The methodological issues among prediction models have been reviewed [3,9−13] and reporting guideline (e.g., TRIPOD) [2] and tools for assessing risk of bias (e.g., PROBAST) [14] also have been published.

Of those, prognostic prediction models, aiming to predict the risk of future outcomes based on a given baseline health state by a statistical progress, represent a highly attended research topic [15−17], and many efforts have been made to popularize and improve the production of prognostic prediction models, including the introduction of its concept, methods, and applications [15,16,18,19]. This is particularly the case for obstetric care, as predicting and preventing adverse outcomes are probably the most interested issues to obstetricians during perinatal care [20].

Obstetric care also represents an advantage area in the production and use of prognostic prediction models. First, the health of mothers and their offspring is usually placed

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* Corresponding author: Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China. Tel.: +86 18980606047; fax: +86 028 85164187.

E-mail address: sunx79@hotmail.com (X. Sun).

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What is new?

Key findings

- The published prognostic prediction models for obstetric care had important limitations in the study design and conduct.
- These limitations may lead to questionable credibility and applicability of such models for obstetric care.

What this adds to what was known?

- Lack of prespecified protocol, absence of validation, inappropriate measurement of outcomes and predictors, unclear intended timing of model use, and insufficient sample sizes are the main limitations of these models.

What is the implication and what should change now?

- Our findings highlighted important methodological gaps and the need to strengthen the use of rigorous methods among those prognostic prediction models for obstetric care.
- The recommendations have been proposed to assist the study design and conduct to improve the model credibility and applicability.

on the top priority of health care systems. As such, both obstetricians and pregnant women have strong desires to foresee any undesirable outcomes during gestation and delivery so as to reduce potential risk during the management of pregnancy. For instance, prognostic prediction models have been developed for managing pregnant women with gestational hypertension-related diseases across different settings [21–23]. Second, many countries have established comprehensive antenatal care systems [24–28], which document a full spectrum of health care data during regular antenatal visits and examinations. This infrastructure, in turn, provides great opportunities for developing prognostic prediction models. Third, as a special population, pregnant women often have a high level of compliance, including scheduled follow-ups and reporting of health information, which ensures data completeness and data accuracy.

Up to now, over 250 prognostic prediction models have been published in obstetric care field [20,29]. However, little is known as to whether those published prognostic prediction models meet the desirable methodological rigors for clinical use. One previous study reviewed a small number of methodological characteristics of those published models, such as target outcomes, inclusion of model validation, and reporting of calibration and discrimination [20]. Nevertheless, many important methodological details about design and conduct were not assessed, and no recommendations are currently available for prognostic prediction models in obstetrics. Therefore, we undertook a thorough and systematic survey to examine methodological characteristics about the design and conduct in prognostic prediction models used for obstetric care.

2. Methods

2.1. Eligibility criteria

We included studies that reported the development and/or validation of a prognostic prediction model in the field of obstetric care, the subject of which involved pregnant women, laboring, postpartum women, and neonates aged within 2 years after delivery. A prognostic prediction model was defined as a multivariable model, predicting risk of specific outcomes occurring in future by selected predictors [15,16].

Studies were excluded if they met any of the following: (1) the study was a diagnostic prediction model, defined as a prediction model used to estimate the risk of specific outcomes at present; (2) the predicted outcome was beyond the area of obstetrics (e.g., in vitro fertilization, gynecologic tumor, and menopause); (3) the study aimed to assess the contribution of specific predictor(s); (4) the study exclusively assessed the impact of a prediction model; or (5) the study was a review, comment, letter or editorial, protocol, or conference abstract. We excluded diagnostic prediction models mainly because the focus of diagnostic model were on imaging prediction in the field of obstetric care and diagnostic prediction models are substantially different from prognostic prediction, especially in study design, data source, and other considerations.

2.2. Literature search

We searched PubMed to identify eligible articles published in selected journals from January 1, 2011 to February 28, 2018. These journals included the six top general medicine journals (*NEJM*, *Lancet*, *JAMA*, *BMJ*, *Ann of Intern Med*, *and PLoS Med*) and top specialty journals defined as the top 15% journals according to the impact factor of the Science Citation Index for Obstetrics and Gynecology in 2016 (Supplementary Table 1). In developing the search strategy, we included MeSH terms and free-text keywords regarding obstetrics. Besides, we adopted a validated search filter for prediction model, which showed good sensitivity and specificity [30]. The search language was limited to English.

2.3. Study process

Teams of paired investigators (Y.Q., G.Z., Q.H., and C.L.), trained in clinical epidemiology or biostatistics with practical skills of prediction models, undertook the study selection. Guided with structured, pilot-tested forms, they independently screened titles and abstract, as well as full

texts using the predefined eligibility criteria. Then, two of the investigators (Y.Q. and C.L.) independently collected the data from each eligible study, using a prespecified questionnaire. The teams of two investigators checked for consistency, and any disagreements were resolved by discussion, otherwise adjudicated by a third reviewer (J.T.).

2.4. Development of the study questionnaire

We developed a structured questionnaire for collecting data from the included prognostic prediction models. Initially, we prepared a preliminary questionnaire form based on the items from the published statements and tools about prediction models (e.g., PROGRESS [15,16,18,19], CHARMS checklist [31], TRIPOD statement [2], and QUIPS tool [32]). Then, we convened seven experts in clinical epidemiology, biostatistics, and obstetrics to brainstorm for additional items. The group of experts subsequently undertook focused discussion to assess the relevance and appropriateness of candidate items and refined the wording of each item. Using the questionnaire, three investigators (J.T., Y.Q., and C.L.) conducted a pilot test to evaluate the completeness, appropriateness, and feasibility.

2.5. Data collection

We collected data from the included studies. If more than one prediction model was reported in a study, we chose the model that was claimed as the primary one by the authors; otherwise, we chose the first reported model.

We collected the following general information from each study, including publication year, country of first author, involvement of any epidemiologist or statistician, whether it was a multicenter study, and source of primary funding (public, private, no funding/unclear), and availability of protocols (published; unpublished but mentioned in the main study; not reported). We judged that an epidemiologist or statistician was involved if any author was affiliated with the department of epidemiology or statistics or if a person with expertise in epidemiology or statistics was clearly acknowledged (Supplementary Table 2). Primary funding was the first acknowledged funding in the article.

We also documented the study purpose, intended timing of model use (reported and not reported), whether eligibility criteria were clearly described (yes or no), participant recruitment (random selection, consecutive recruitment, nonrandom recruitment, others, or not reported), epidemiological design (retrospective cohort, prospective cohort, nested case-control study, case-control study, others), data sources (cohort with specific question, electronic medical records [EMRs] database or medical charts, registry database, trial data, claims database, or others). We categorized study purpose as follows: (1) developing a new prediction model without internal validation, (2) developing a new prediction model with internal validation only, (3) developing a new prediction model with external validation only, (4) developing a new prediction model with both internal and external validation, (5) external validation, without updating a prediction model, and (6) external validation, with updating a prediction model (Supplementary Table 2).

We further documented the outcome of interest, whether it was a composite outcome, type of the outcome (continuous, binary, categorical, or time to event outcome), clear criteria used for ascertaining the outcome (yes, no, or not reported), consistent measurement of the outcome across all participants (yes, no, or not reported), blinded assessment of the outcome; as well as type of predictors (routine clinical variables plus research-oriented biomarkers; routine clinical variables only) and details of intervention reported if included as a predictor (yes, no, not applicable). We

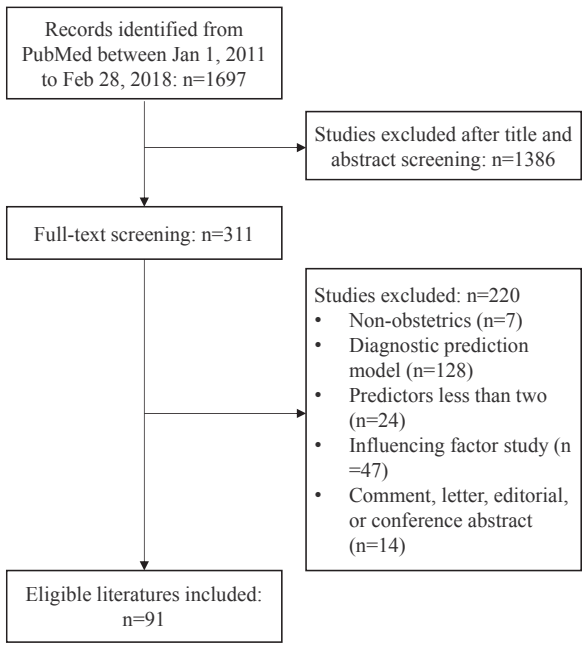

Fig. 1. Flow chart of study selection.

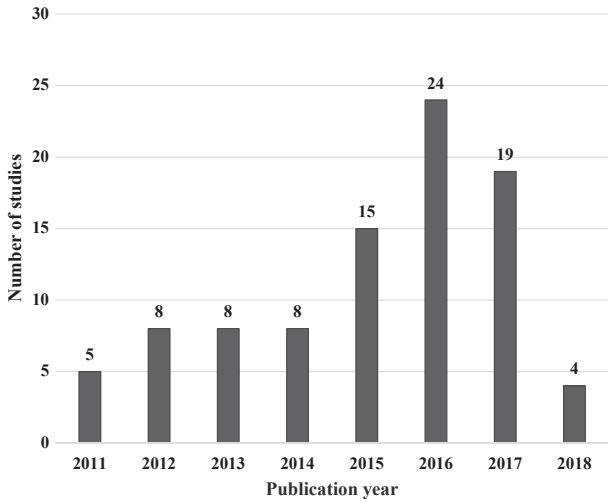

Fig. 2. Publication counts of prognostic prediction models for obstetric care from January 2011 to February 2018.

Table 1. General characteristics about design and conduct of prognostic prediction models

Characteristics	Number (%)
Country of first author	
The United Kingdom	28 (30.77)
The United States	17 (18.68)
Spain	17 (18.68)
Others	29 (31.87)
Multicenter study	
Yes	47 (51.65)
No	41 (45.05)
Unclear	3 (3.30)
Involvement of an epidemiologist or a statistician	
Yes	20 (21.98)
No	70 (78.02)
Primary source of funding	
No funding	30 (35.16)
Public funding	29 (31.87)
Private funding	30 (33.97)
Unclear	2 (2.20)
Publication of study protocol	
Protocol published	18 (19.78)
Unpublished	1 (1.10)
Not reported	72 (79.12)
Study purpose	
Develop a model without validation	53 (58.24)
Develop a model with internal validation	27 (29.7)
Develop a model with external validation	3 (3.30)
Develop a model with both validations	1 (1.10)
External validation with updating	2 (2.20)
External validation without updating	5 (5.49)
Intended timing of use	
Reported	71 (78.02)
Not reported	20 (21.98)
Eligibility criteria clearly described	
Yes	63 (74.73)
No	23 (25.27)
Participant recruitment method	
Consecutive recruitment	36 (39.56)
Nonrandomized enrollment	4 (4.40)
Random selection	1 (1.10)
Not reported	50 (54.95)
Epidemiological design	
Prospective cohort	58 (63.74)
Retrospective cohort	12 (13.19)
Nested case-control study	11 (12.09)
Case-control study	5 (5.49)
Unclear	5 (5.49)
Data sources	
Classical cohort study	59 (64.84)
EMR or medical chart	14 (15.38)
Registry	9 (9.89)
Other[a]	9 (9.89)

Abbreviation: EMR, electronic medical records.

[a] Other data source included secondary analysis of clinical trial data (4 studies), observational study (1 study), and unclear (4 study).

additionally documented the number of participants recruited in analysis, number of participants used for model development, internal validation and external validation, number of candidate predictors included in model, number of predictors finally included in model, and number of events (Supplementary Table 2) and also calculated the number of events per variable (EPV) for predictors included in model.

2.6. Statistical analysis

Quantitative data were summarized by mean and standard deviation if normally distributed, otherwise by median and interquartile range (Q_L–Q_U). Categorical variables were expressed as the number of frequencies and proportion.

3. Results

Our search yielded 1,697 records from PubMed. After reading titles and abstracts, 1,386 records were excluded. On reviewing full texts of 311 articles, 91 studies were included in our analysis (Fig. 1).

Among those studies, 44 (48.4%) were published before 2016, and the publications of models increased over years (Fig. 2); only two (2.2%) were published in the top general medicine journals, and the remaining (97.8%) in major specialty journals; most (68.1%) were conducted in the United Kingdom, the United States, and Spain; 47 (51.7%) were multicenter studies; 20 (22.0%) involved at least one epidemiologist or statistician; and 59 (64.8%) had financial support, with 29 (31.9%) from public funding. Only 18 (19.4%) studies published study protocols (Table 1).

Of those 91 studies, 53 (58.2%) developed a new model without any validation, and only one (1.1%) developed the model with both internal and external validations; 20 (22.0%) did not clearly mention the intended timing of use; 23 (25.3%) did not clearly describe eligibility criteria; 50 (55.0%) did not describe the method of participant recruitment (Table 1).

In total, 70 (76.9%) studies used cohort study design (58 prospective and 12 retrospective), and 16 (17.6%) chose case-control design; 59 (64.8%) used data from cohort studies with specific research questions, 14 (15.4%) from EMR or medical charts, and nine (9.9%) from patient registries (Table 1).

Table 2. Outcomes and predictors of prognostic prediction models

Outcomes and predictors	Number (%)
Primary outcome of interest	
Composite of adverse prenatal outcomes	9 (9.89)
Stillbirth or miscarriage	8 (8.79)
Cesarean section	8 (8.79)
Pre-eclampsia	6 (6.59)
Shoulder dystocia	3 (3.30)
Large for gestational age	3 (3.30)
Fetal growth restriction	3 (3.30)
Composite of adverse maternal outcomes	2 (2.20)
Maternal mortality	2 (2.20)
Birth weight	2 (2.20)
Gestational diabetes mellitus	1 (1.10)
Ectopic pregnancy	1 (1.10)
Other outcomes[a]	8 (8.79)
Was it a composite outcome?	
Yes	14 (15.38)
No	77 (84.62)
Type of the outcome	
Binary	84 (92.31)
Continuous	6 (6.59)
Categorical	1 (1.10)
Clear criteria used for ascertaining outcome	
Yes	76 (83.52)
No	0 (0.00)
Not reported	15 (16.48)
Consistent measurement of outcomes among all participants	
Yes	61 (67.03)
No	2 (2.20)
Not reported	28 (30.77)
Blinded assessment of outcomes	
Yes	22 (24.28)
No	69 (75.82)
Type of predictors	
Routine clinical variables	52 (57.14)
Routine clinical variables plus research lab-based biomarkers	39 (42.86)
Details of intervention if included as predictors	
Reported	3 (3.30)
Not reported	1 (1.10)
Not applicable	87 (95.60)

Abbreviations: EP, ectopic pregnancy; SAB, spontaneous abortion; IUP, intrauterine pregnancy.

[a] Other outcomes included delivery within 7 days of transvaginal cervical length (TVCL), escape RBC transfusion, fetal middle cerebral artery plasticity index (MCA-PI), first trimester pregnancy location (EP vs. SAB + IUP), infant hypertension, and arterial remodeling in intrauterine growth restriction, maternal serum alpha-fetoprotein (AFP) in the first trimester, severe right ventricular outflow tract obstruction (RVOTO), and success of the expectant management.

Preterm delivery (19, 20.9%), small for gestational age (16, 17.6%), and stillbirth or miscarriage (8, 8.8%) were the three most frequently used outcomes. Of those, 14 (15.4%) studies used a composite outcome (e.g., adverse prenatal outcomes), and most studies (84, 92.3%) chose a binary outcome; 15 (16.5%) did not clearly describe the criteria used for ascertaining outcome, and 30 (30.8%) did not report methods for outcome measurement; 22 (24.3%) used blinded assessment of primary outcome; and 52 (57.14%) exclusively used routine clinical variables for predictors (Table 2).

The median sample size was 1,269 (interquartile range, 385–7,816). The smallest study only included 80 participants, and 11 (12.1%) models have sample sizes less than 200. The number of predictors finally included in models ranged from 2 to 16, and nearly half of the studies (44, 48.4%) included four or fewer predictors. The median number of events was 104 (56–243), and 41 (48.8%) had the number of events fewer than 100. The median number of EPV was 20.4 (9.93–44.58), and 19 (24.7%) had the EPV less than 10 (Table 3).

In the comparison of models published before 2016 vs. those published in 2016 or later, no statistically significant differences were found in nearly all of the characteristics.

4. Discussion

4.1. Summary study findings and implications for future study

In this study, we found that most failed to include any information about model validation, and very few included external validation. A relatively large proportion of studies did not state intended timing of model use, failed to state eligibility criteria, and did not include details about how outcomes were ascertained and measured. Most of the studies failed to perform blinded assessment of outcomes. Nearly half were derived from a single-center study, and a relatively large proportion of studies chose to use retrospective data. We also found that a relatively large proportion of studies had small number of sample sizes and the number of EPV was relatively small, which result in models being underpowered, and regression coefficients being possibly biased [33–35].

The current practice has highlighted important methodological limitations when planning and conducting the model studies. However, our assessment about the methodological details was primarily based on reporting. There might be cases that the investigators had considered the methodological issues but did not clearly report. This situation also stressed the importance of complete reporting.

In light of future studies on prognostic prediction models for obstetric care, one should consider involving methodologists in the planning and conduct of the studies. Prospective designs and a study at multicenter setting are preferred. The number of participants and events should be carefully planned, both for model development and validation.

Table 3. Number of participants, events, and predictors for prognostic prediction models

Participants, events, and predictors	Numbers (%)
Number of participants included in modeling analysis (N = 91)	
Min–Max	80~79,559
Median (P_{25}–P_{75})	1,269 (385~7,816)
<200	11 (12.09)
200~999	29 (31.87)
≥1,000	51 (56.04)
Number of participants used for model development (N = 84)	
Min–Max	48~76,897
Median (P_{25}–P_{75})	1,050 (370~7,279)
<200	14 (16.67)
200~999	27 (32.14)
≥1,000	43 (51.19)
Number of participants used for internal validation (N = 28)	
Min-Max	165~24,184
Median (P_{25}–P_{75})	603 (359~1,184)
<200	3 (10.71)
200~999	18 (64.29)
≥1,000	7 (25.00)
Number of participants used for external validation (N = 11)	
Min–Max	169~79,559
Median (P_{25}–P_{75})	1,805 (355~46,328)
<200	1 (9.09)
200~999	4 (36.36)
≥1,000	6 (54.55)
Number of candidate predictors included in model (N = 80[a])	
Min–Max	2~54
Median (P_{25}–P_{75})	9 (5~16)
2~4	20 (21.98)
5~9	26 (28.57)
10~14	19 (20.88)
15~19	12 (13.19)
≥20	14 (15.38)
Number of predictors finally included in models (N = 91)	
Min–Max	2~16
Median (P_{25}–P_{75})	5 (3~7)
2~4	44 (48.35)
5~9	39 (42.86)
10~14	7 (7.69)
15~19	1 (1.10)
Number of events (N = 84[b])	
Min–Max	9~4,468
Median (P_{25}–P_{75})	104 (56~243)
<100	41 (48.81)
100–499	38 (45.24)
≥500	5 (5.95)
Number of events per variables (N = 77[c])	
Min–Max	1.00~744.70
Median (P_{25}–P_{75})	20.40 (9.93~44.58)
<10	19 (24.67)
10–19	18 (23.38)
≥20	40 (51.95)

Abbreviation: EPV, events per variable.

[a] 11 models did not report this information.

[b] 6 model adopted linear regression, and 1 model did not report this information.

[c] 6 is linear regression model, and the other lacks key information to calculate EPV.

Explicit intended timing is always warranted to develop or validate a prognostic prediction model. One should also prespecify the outcomes of interest and clearly define and measure such outcomes [36,37]. This is particularly the case as some outcomes in obstetrics, such as small for gestational age and pre-eclampsia, have varying definitions, and measurements may differ across settings. In addition, blinded assessment of outcome is always desirable, particularly when judgment is involved for assessing outcomes.

One should always consider validating the predictions models, as both model development and validation are essential processes for establishing a useful prediction model [38]. The model performance from internal validation may often be more optimistic than the underlying truth [2,39]. Techniques for internal validation, such as bootstrapping, cross-validation, and split-sample validation, are recommended to achieve a more honest estimate of performance [38,40]. More importantly, external validation should always be considered in the validation of a model [41].

In further improving the usefulness of model, one should also consider publishing study protocols, which prespecify all important methodological details. These should at least cover study rationale and overall design, data source, eligibility criteria, method for participant recruitment and data collection, definition and measurement of outcomes and predictors, number of participants, and events planned for model development and/or validation.

4.1.1. Comparison with other studies

A number of studies have systematically reviewed methodological issues about study design and conduct among prediction models [3,42–44]. Among those, a few examined methodological issues across disease areas. For instance, Bouwmeester et al. [44] investigated the study methods of 71 articles published in six high-impact journals and found that the study design was unclear in 15% of studies. Collins et al. reviewed the reporting of external validation by evaluating 120 prediction models [31] and found that the vast majority of studies failed to report the key details of external validation, such as study design,

the number of outcome events, and model calibration [3]. Whittle et al. [42] examined measurement error and timing of predictor values among 151 predictors reported in 33 studies; the results showed that 51 (33.7%) predictors were categorized as high risk of error, and merely 8 (24.2%) studies explicitly stated the intended timing of model use and when the predictors were measured.

Several studies investigated methodological issues in specific disease areas. However, only one systematically reviewed prognostic models in obstetrics, while the methodological details about study design and conduct were little investigated [20]. The other studies examined issues in areas including cancer [45,46], cardiovascular diseases [1,35], chronic kidney disease [47,48], diabetes [33,49,50], traumatic brain injury [34,51], skin disease [52], and reproductive medicine [53]. Similar methodological limitations were found in these specialty areas. For instances, several reviews found that lack of internal validation was common [51,52,54]. Even in high-impact general medicine journals, most were internally validated only [55]. A relatively small proportion of studies clearly defined the intended timing for using the models, and many did not assess the outcome in a blinded manner [55]. The number of EPV remained small [33,35]. Such findings were consistent with our studies.

4.2. Strengths and limitations

To the best of our knowledge, this is the first systematic survey that exclusively assessed the design and conduct of prognostic prediction models used for obstetric care. In this study, we included a representative sample of prognostic prediction models. We used rigorous methods to develop a structured questionnaire specifically for prognostic prediction models in obstetrics. We carefully selected studies and collected data from included studies.

There also are two limitations. First, our study did not include all published prognostic prediction models for obstetric care; however, one may be reassured that the prognostic prediction models for obstetric care published in other journals would not be superior. Second, we did not report the statistical details about those published prognostic prediction models because of space limitation; we will report this in a subsequent article.

5. Conclusion

In conclusion, although the number of prognostic prediction models for obstetric care has increased rapidly in the past several years, several important issues jeopardize the effective use of these models, such as lack of prespecified protocol, absence of validation, inappropriate measurement of outcomes and predictors, unclear intended timing of model use, and insufficient sample sizes. Substantial efforts are warranted to strengthen the use of rigorous methods for prognostic prediction models for obstetric care.

CRediT authorship contribution statement

Jing Tan: Conceptualization, Writing - original draft. **Yana Qi:** Data curation, Formal analysis. **Chunrong Liu:** Data curation, Investigation. **Yiquan Xiong:** Formal analysis. **Qiao He:** Investigation. **Guiting Zhang:** Investigation. **Meng Chen:** Resources. **Guolin He:** Resources. **Wen Wang:** Writing - review & editing. **Xinghui Liu:** Resources. **Xin Sun:** Conceptualization, Writing - review & editing.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.07.009.

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