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Key Points from 3rd Clinical Epidemiology Workshop, 18 – 20th Oct 2022
November 2022
Vol. 2 Issues 19
Page 453

PROGNOSTIC RESEARCH

By: Nurfaizah Saibul

PROGNOSTIC RESEARCH

What?
- What is the prognosis of the patient regardless or without treatment?
- Broad domain: Patients presenting with a certain disorder in a certain setting.
- E.g. Framingham Risk Score and Apgar Score.

Why?
- Inform patients and physicians about future health.
- Guide medical and personal action.
- **Answer questions about the future course of the disease:** *What is the prognosis if you don't treat it?*
- **Choosing treatment options:** *Is a patient 'healthy' enough for a certain type of surgery?* **-> risk factors**

How?
- Adhere to prognosis setting in practice.
- **Starting point for prediction:**
  -> After diagnosis.
  -> After specific surgery.
  -> After treatments are finalized (cancer therapy).
- **How do we use determinants to predict prognosis?**
  -> Scoring system
  -> Risk model
  -> Prediction model
  -> Risk stratification model

Longitudinal design

Population with a certain health/ disease status → **Determinants/ Predictors:** -Demographic data -Disease characteristics -Specific markers → **Outcome**

T=0 — End of follow up

Domain: Everyone for whom the results should apply to.
Study population:
Sample from your domain (representative sample)

Determinants/ Predictors:
Risk factors
(from clinical knowledge, literature)

Outcome:
-Mortality
-Recurrence of the disease
-Complications

DDO:
-Domain
-Determinants
-Outcome

Setting

Time/ Follow up

Research Questions

Predict the **absolute risk (AR)** of a certain **health/disease outcome** within a **specified time** with easily and safely **available data (predictors)** from a patient.

Research question from clinical practice or gap of knowledge

E.g. What is the risk of developing restenosis after a coronary intervention?

Study design

Descriptive:
-X explanatory
-X causality
-X confounding issues

Observational:
No manipulation of determinants.

Follow up:
Cohort
Exposure is present before the outcome.

No. of determinants:
> 1

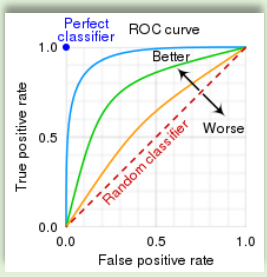
Data Analysis

Evaluate available data per patient

- **Describe association between determinant and outcome.**
- **Univariable analysis of determinant -> outcome association**
  - Select predictors ($p < 0.20$).
- **Multivariable analysis combining the predictors in 1 model:**
  - Independent influence of predictor
  - Adding predictors stepwise
  - ROC Curve
- **Transform model to a risk score -> Predictive value.**

Reporting

- **Univariable predictor analysis**
- **Multivariable predictor analysis:**
  -ROC Curve
  -Risk table with the predictive value of the evaluated determinants/ predictors
- **Transparent Reporting of a Multivariable Prediction model for Individual Prognosis or Diagnosis (TRIPOD)**



ROC Curve:
-Only for research purposes.
-Does not provide predictive value.
-Likelihood of classifying a patient in the correct category: with or without disease.
-Good model: ROC curve ~ 1
-The higher the curve, the better the model.

November 2022
Vol. 2 Issues 19
Page 454

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PRAGMATIC TRIALS AND REAL-WORLD EVIDENCE

By: Iman Hafizah

Pragmatic trials offer the opportunity to obtain **real-world data** on the relative effectiveness of a treatment in an early phase of development, thus addressing the need for real-world evidence. They intent to explore the effectiveness of a new drug or treatment in day-to-day clinical practice without altering the normal patient and physician behaviour.

Why pragmatic trials?

- Aims at validly capturing the full effect of a treatment strategy in the real world.
- Pragmatic trials aim to evaluate many interventions and compare their effectiveness.
- Examine treatment effects of many interventions in a plethora of settings, large sample sizes and long follow-up periods are dictated in order to produce reliable and (re)usable evidence.

Pragmatic trials vs randomised controlled trials

Heterogenous patient population	Homogenous patient population
Assess during routine clinical care	Assess during trial specific visit
Flexible adherence to protocol	Strict adherence to protocol
Provides real-world data	Provides efficacy and safety data from a controlled study

Pragmatic trial design

There are four domains that should be considered:

Study population

Study setting

Intervention vs chosen comparator

Outcome measure

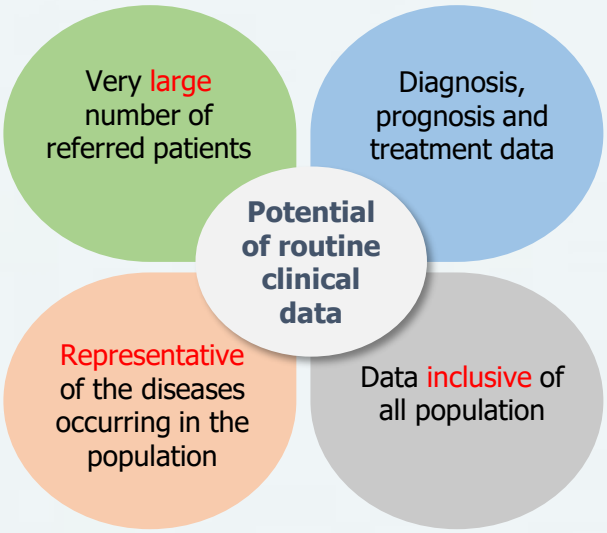
> Real-world data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources."
>
> So data that are not collected in the context of highly-controlled RCTs

For further reading on pragmatic trials and real-world evidence, do check out the series of articles [HERE] by the Journal of Clinical Epidemiology

REGISTRY-BASED TRIALS

Evidence may also come from 'real world data' collected in routine clinical practice. These data can be collected from hospital visits and electronic medical record databases derived from routine measurements of follow-up.

Why registry-based trials?

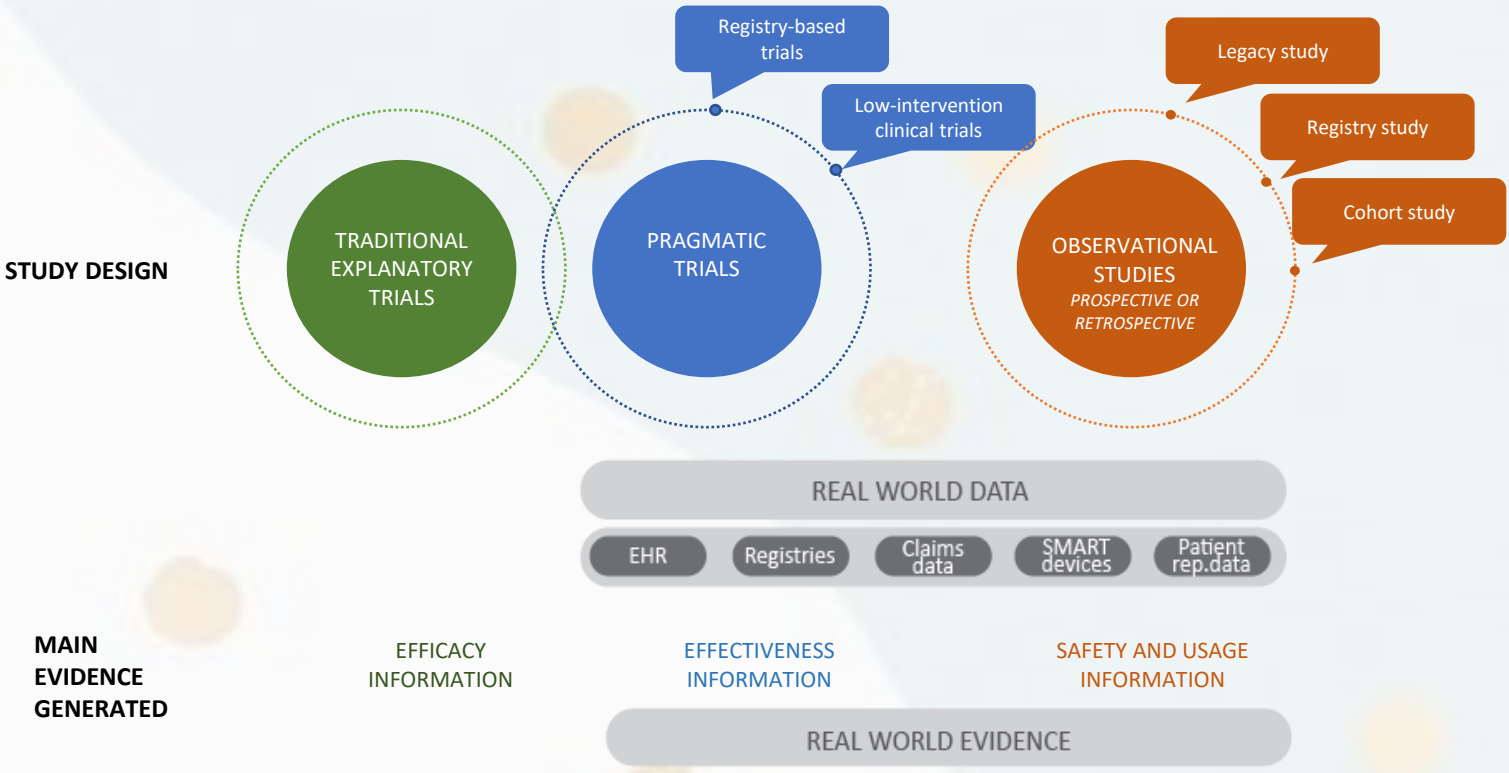


Challenges of registry-based data

1. Missing information
2. Unstructured information
3. Absence or limited follow-up data

Do check if your real-world data fit the criteria for methodological and operational aspects of the study

Designing trials using real-world evidence



Source: juliusclinical.com

To read more on the implementation of real-world evidence into practice, click [HERE]

November 2022
Vol. 2 Issues 19
Page 456

APPLICATION OF DIAGNOSTIC STUDIES RESULTS TO CLINICAL PRACTICE

By Salwana Ahmad

Diagnostic Research

A diagnosis is an identification of a disease/outcome via examination present at this moment. The fundamental purpose of a diagnostic study is to reduce uncertainty about the presence or absence of the disease in order to reduce the risks of an improper treatment decision.

Diagnostic Predictive Factors

A unique combination of predictors, clinical and non-clinical characteristics such as the individual's demographics, history taking, physical and clinical examination, disease characteristics, laboratory or imaging test results.

Diagnostic Predictive Model

Decision-making tool for the clinician, to provide for estimating the absolute probability (risk) of having a certain outcome (e.g. disease, event, complication) in an individual, given diagnostic predictive factors to aid clinical decision-making.

STUDY TYPE: Observational study – cross-sectional & descriptive. It can be a sub-part of a longitudinal study.

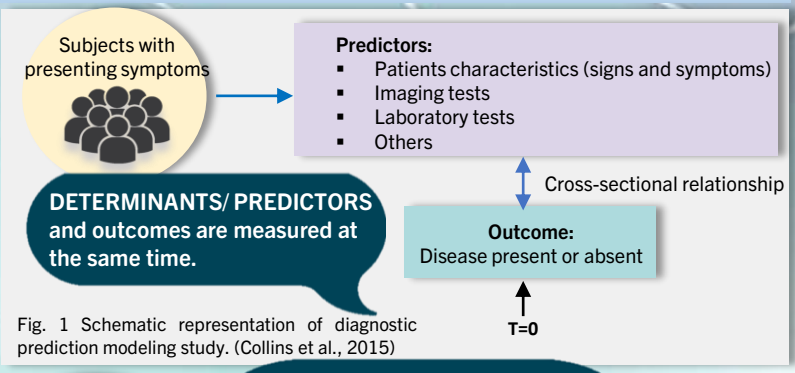
Primary

Predicting bacterial cause in infectious conjunctivitis: cohort study on informativeness of combinations of signs and symptoms

Remco P Rietveld, Gerben ter Riet, Patrick J E Bindels, Jacobus H Sloos, Henk C P M van Weert

The bacterial cause of acute infectious conjunctivitis

1. Many unnecessary ocular antibiotics are prescribed due inability of most general practitioners to discriminate between a bacterial and a viral cause.
2. The culture of the conjunctiva is seldomly done, mostly because of the resulting delay.



DETERMINANTS/ PREDICTORS and outcomes are measured at the same time.

Fig. 1 Schematic representation of diagnostic prediction modeling study. (Collins et al., 2015)

1. SUBJECTS PRESENTED WITH ELIGIBILITY CRITERIA
Patients with red eye and either (muco)purulent discharge or sticking of the eyelids at care centers

Define DOMAIN well: Setting (Emergency Department/Care Center), study population with suspicion of a certain disease.

Ideal situation: solid diagnosis without the use of reference test and faster.

2. RESEARCH QUESTION
To find an efficient set of diagnostic of a bacterial origin of acute infectious conjunctivitis.

Easy, to follow the diagnostic in daily practice, more than 1 test, from less to more invasive tests.

3. DETERMINANTS/PREDICTORS
Collected through a standardized questionnaire, physical examinations (Index Test) and Standard Reference from the diagnostic investigations.

Medical history taking

- History of hay fever, conjunctivitis, and allergic conjunctivitis.
- Duration of symptoms (days).
- Self-medication & self-treatment – cleaning with water.
- Symptoms – itching, burning sensation, foreign body sensation.
- Numbers of glued eyes in the morning (none, one or two eyes)

Physical examination

- Degree of redness (peripheral, whole conjunctiva, or whole conjunctiva and pericorneal)
- Presence of periorbital oedema,
- Secretion/discharge (watery, mucous, or purulent).
- Bilateral involvement (yes or no)

Reference Standard

- One conjunctival sample of each eye for a bacterial culture

OUTCOME: Real presence/absence of disease, using the determinants of interest (index test)

Without knowledge of the outcome. Use the same methodology as in daily practice.

Reference test is often:

- **Nonethical (burden/risk)**
- **Inefficient (expensive/delayed)**

4. MAIN OUTCOME MEASURES
Probability of positive bacterial culture, given different combinations of index test results; area under receiver operating characteristics curve

5. BLINDED
The general practitioners did not receive the culture results, and the microbiologist who analyzed the cultures had no knowledge of the results of the index tests.

STATISTICAL ANALYSIS:

1. Estimate the prior risk-prevalence in the study population based on the reference test.
2. Univariate (table 2x2): Compare the outcome of every single test with the reference test.
3. Multivariate - via model comparing a set of tests with reference test),

6. STATISTICAL ANALYSIS

- **Used stepwise forward logistic regression analysis** to assess the association between findings from the index test and the presence of a positive bacterial culture in the study eye.
- Model with variables with a **Univariate P value of ≤0.10**
- **Multivariate P value of <0.15** (independent indicators of the presence of bacteria and retained in the final model)

SAMPLE SIZE:
Rule of thumb '1 on 10'. Per determinants of investigation, a minimum of 10 subjects with a positive outcome

RESULT:

1. Prior risk (prevalence).
2. Discrimination model (ROC curve)
3. Calibration model (Hosmer-Lemeshow goodness of fit test.
4. Applicable diagnostic score with accompanying posterior risk.

7. RESULT.

Table 3

Results of logistic regression analysis. Independent indicators of positive bacterial cul… their clinical score

Indicator	Odds ratio (95% CI)	Regression coefficient	Clinical score*
Two glued eyes	14.99 (4.36 to 51.53)	2.707	5
One glued eye	2.96 (1.03 to 8.51)	1.086	2
Itching	0.54 (0.26 to 1.12)	−0.61	−1
History of conjunctivitis	0.31 (0.10 to 0.96)	−1.161	−2
Area under ROC curve (95% CI)	0.74 (0.65 to 0.82)	-	-

ROC=receiver operating characteristic

*Clinical scores of every symptom pre… a patient with two glued eyes, itch, and no history of conjunctivitis has a clinical score of: 5 + −1 = 4.

- Prevalence of positive culture in this study=32% (57/177) is higher than a minimum sample size needed.
- 4 determinants x 10 subjects = a minimum of 40 subjects with a positive culture.

Table 3: the odds ratios of these independent indicators of a positive bacterial culture and their clinical scores.

Model performance measure and quantification of the final model:

- Overall **prior risk** (**prevalence**) **of positive culture=32%** (57/177).
- **3 determinants** were retained in the multivariable regression analysis: **history of conjunctivitis** (yes or no), **itch** (yes or no), and **glued eyes in the morning** (0, 1, or 2).
- **Ability to discriminate between patients with and without a positive bacterial culture** using the area under the receiver operating characteristics curve = **AUC 0.74** (95% confidence interval 0.65 to 0.82).
- **The reliability or calibration** using the **Hosmer-Lameshaw good-ness of fit test ad a P value of 0.117**, indicating that the model does not misrepresent the data.
- **Validation of the model using bootstrapping technique** showed hardly any indication of undue influence by particular patients (corrected 95% confidence interval of the area under **curve 0.63 to 0.80**).

7. RESULT.

Clinical scores and their associated probabilities of a positive culture, sensitivity, and specificity

Clinical score	Percentage (No) observed positive cultures*	Percentage (95% CI) predicted positive cultures†	Percentage correctly treated (sensitivity)‡	Percentage correctly untreated (specificity)§
+5	100 (5/5)	77 (57 to 90)	9	100
+4	71 (17/24)	65 (47 to 79)	39	94
+3	0 (0/3)	51 (23 to 79)	39	92
+2¶	41 (16/39)	40 (26 to 55)	67	73
+1	20 (10/51)	27 (17 to 39)	84	38
0	13 (3/23)	18 (7 to 38)	89	22
−1	20 (5/25)	11 (4 to 26)	98	5
−2	0 (0/1)	7 (2 to 28)	98	4
−3	17 (1/6)	4 (1 to 15)	100	0

*Overall prevalence of positive culture=32% (57/177). In parenthesis are the number of positive cultures (numerator) and total number of cultures (denominator) in that row.
†Predicted probability is the probability of a positive culture calculated by regression analysis.
‡Fraction of patients with a positive culture who would be correctly treated if the clinical score in that row was used as treatment cut-off point.
§Fraction of all patients with a negative culture who would be correctly untreated if the clinical score in that row was used as treatment cut-off point.
¶Clinical score of +2 used in the text to illustrate its use for treatment decisions.

- The **treatment cut-off point is set at +2**, indicating that only patients with a **clinical score of +2 or higher receive ocular antibiotics, 38/57 (67%) of patients** are correctly treated and 87/120 (73%) patients are correctly untreated.
- A treatment **cut-off point of +2 to** illustrate an **approximate reduction of antibiotic prescriptions from more than 80% to 40%.**
- If applied to the study population, the cut-off point of +2 would lead to a reduction in prescriptions of antibiotics from more than 80% (current practice) to 40% (71/177).

EXTERNAL VALIDATION:
Discrimination and calibration were done with another setting.

DISCUSSION

- This study indicates that in the absence of "alarm symptoms" the decision whether to prescribe antibiotics could be made without any additional diagnostic tests.
- When replicate this study in daily practice, several factors need to be aware such as exclusion patients' criteria, proper instruction to general practitioners, and different outcome in different setting and population.

REPORTING:
Follow 'Standards for Reporting of Diagnostic Accuracy' (STARD-2015)

The summary of this article is adapted from (Rietveld et al., 2004). Predicting bacterial cause in infectious conjunctivitis: cohort study on the informativeness of combinations of signs and symptoms. The key points was based on the 3rd Clinical Epidemiology Workshop: Diagnostic and Prognostic Research organized by National Institutes of Health (NIH) 18-20th October 2022.

1. Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. M. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. *BMJ (Online)*, *350*. https://doi.org/10.1136/bmj.g7594
2. Rietveld, R. P., ter Riet, G., Bindels, P. J. E., Sloos, J. H., & van Weert, H. C. P. M. (2004). Predicting bacterial cause in infectious conjunctivitis: Cohort study on informativeness of combinations of signs and symptoms. *British Medical Journal*, *329*(7459), 206–208. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC487734/