

## Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care

By the members of the International Working Group on Chest Pain in Primary Care (INTERCHEST)

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### Abstract

**Objective:** To construct a clinical prediction rule for coronary artery disease (CAD) presenting with chest pain in primary care.

**Study Design and Setting:** Meta-Analysis using 3,099 patients from five studies. To identify candidate predictors, we used random forest trees, multiple imputation of missing values, and logistic regression within individual studies. To generate a prediction rule on the pooled data, we applied a regression model that took account of the differing standard data sets collected by the five studies.

**Results:** The most parsimonious rule included six equally weighted predictors: age  $\geq 55$  (males) or  $\geq 65$  (females) (+1); attending physician suspected a serious diagnosis (+1); history of CAD (+1); pain brought on by exertion (+1); pain feels like “pressure” (+1); pain reproducible by palpation (−1). CAD was considered absent if the prediction score is  $< 2$ . The area under the ROC curve was 0.84. We applied this rule to a study setting with a CAD prevalence of 13.2% using a prediction score cutoff of  $< 2$  (i.e., −1, 0, or +1). When the score was  $< 2$ , the probability of CAD was 2.1% (95% CI: 1.1–3.9%); when the score was  $\geq 2$ , it was 43.0% (95% CI: 35.8–50.4%).

**Conclusions:** Clinical prediction rules are a key strategy for individualizing care. Large data sets based on electronic health records from diverse sites create opportunities for improving their internal and external validity. Our patient-level meta-analysis from five primary care sites should improve external validity. Our strategy for addressing site-to-site systematic variation in missing data should improve internal validity. Using principles derived from decision theory, we also discuss the problem of setting the cutoff prediction score for taking action. © 2016 Elsevier Inc. All rights reserved.

**Keywords:** Chest pain; Individual patient data meta-analysis; Myocardial ischemia; Medical history taking; Symptom assessment; Primary health care; Sensitivity and specificity

**Conflict of interest:** The authors declare that they have no competing interests. H.S. is an employee of the Patient-Centered Outcomes Research Institute (PCORI). This study does not describe any policies of PCORI.

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**What is new?****Key findings**

- INTERCHEST collaborators provide a clinical prediction rule for estimating the probability of coronary artery disease in patients presenting with chest pain in primary care.
- It is the first patient-level meta-analysis of clinical prediction rules for chest pain in primary care.

**What this adds to what was known?**

- We present a model for the analysis of a large data set comprised of smaller data sets from different sites.
- The model directly addresses the attendant problems of missing data within sites and different data sets across sites.
- We believe our approach will occupy a secure place in the methodology of developing clinical prediction rules from “big data.”
- Our prediction rule raises a very important methodological question: how to set the cut-off disease score for taking action as if the patient had (or did not have) the target disease.
- Based on decision theory, we point out the main principles that should drive the choice of a threshold.

**What is the implication, what should change now?**

- A key to individualized care is to classify the patient’s probability of a disease or the probability of responding to one of several treatment options.
- This process requires clinical prediction rules that are both internally and externally valid.
- The growth of large data sets based on electronic health records from diverse sites creates opportunities for developing clinical prediction rules, but investigators must pay close attention to methods for dealing with missing clinical data.
- We discuss this problem, and our analytic strategy addresses it directly.

**1. Introduction**

Applying individual patient meta-analysis to create clinical prediction rules is methodologically difficult when primary studies, acting independently, do not collect the same

standard data sets. Methods to summarize the measures of prediction (e.g., regression coefficients) across studies must account for the data that individual studies did not try to collect. We encountered this problem when we used data from five independent studies of chest pain to develop a clinical prediction rule for initial assessment of patients presenting to a primary care setting. Chest pain is an important diagnostic problem in primary care, where 0.7–2.7% of patient encounters are due to chest pain [1–3], and coronary artery disease is the cause of chest pain in 8.6–14.6% of patients [3,4]. Clinical prediction rules developed in emergency departments, specialty clinics, or hospitals may not apply to primary care because diagnostic test results (e.g., an electrocardiogram) are incorporated in the prediction rule in those settings.

**2. Methods***2.1. Data sources and study selection*

We conducted a systematic literature search to identify studies potentially suitable for inclusion in a patient-level meta-analysis [5]. We describe the search and selection process in [Appendix 1](#) at [www.jclinepi.com](http://www.jclinepi.com). We defined primary care as an outpatient or clinic setting other than an emergency department. We identified studies that had prospectively obtained data on symptoms and signs and established a final diagnosis of coronary artery disease (CAD) in consecutive adult patients presenting with chest pain in primary care. We excluded studies if the patients received care in a hospital emergency department or had been preselected for evaluation because of suspected CAD.

We identified eight potentially eligible studies. We did not include three studies because individual patient data were not available [6], we could not contact the principal investigators [7], or the study was ongoing when we conducted our analysis [8] (see [Supplement Fig. 1](#) at [www.jclinepi.com](http://www.jclinepi.com)). The five included studies had a total enrollment of 3,099 patients [2,4,9–11]. [Table 1](#) summarizes characteristics of the studies. All studies had investigated prospectively the diagnostic accuracy of symptoms and signs for CAD in consecutive patients with chest pain in a primary care setting. To establish the final diagnosis, study patients were followed up for a defined period, and study physicians used the clinical course and results of tests to establish the cause of the index episode of chest pain. This delayed-type reference standard can be an acceptable and valid alternative when a single reference test is not possible [12]. The five studies differed in the length of follow-up. The physicians making the final study diagnosis were not blinded to the initial history and physical examination findings.

*2.2. Data management*

Principal investigators of the eligible primary studies were invited to join the INTERCHEST collaboration and

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