Analysis of recruitment in a pragmatic observational study on C-reactive protein point-of-care testing in primary care

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KEY MESSAGES
- This observational study on the implementation of a diagnostic device in routine primary care showed that GPs included 24% of all eligible patients in the original study.
- This selective recruitment resulted in an overestimation of both POC CRP test use and antibiotic prescribing and a biased estimate of the effect of POC CRP on antibiotic prescribing.

ABSTRACT

Introduction: Failure to recruit all eligible study patients can lead to biased results. Little is known on selective patient recruitment in studies on implementation of diagnostic devices.

Objectives: The aim of this observational study was to measure recruitment of patients in an implementation study in primary care on use of point-of-care (POC) C-reactive protein (CRP) and to evaluate recruitment bias and its impact on the study endpoint.

Methods: In a cross-sectional observational study on POC CRP implementation and related antibiotics prescribing, we compared included patients with all eligible patients to assess the representativeness of the included subjects. Eligible patients were adults presenting with acute cough in primary care between March and September 2012. The frequency of POC CRP testing and the proportion of prescribed antibiotics were compared between recruited and non-recruited patients. As measure of bias, odds ratios (ORs) with accompanying 95% confidence intervals (CIs) for the association between CRP level (<20 mg/l or not) and antibiotic prescribing were computed.

Results: Of all 1473 eligible patients 348 (24%) were recruited. In recruited patients, POC CRP tests were conducted and antibiotics prescribed more frequently as compared to non-recruited patients (81% versus 6% and 44% versus 29%, respectively). The ORs were 18.2 (95%CI: 9.6–34.3), 30.5 (95%CI: 13.2–70.3) and 3.8 (95%CI: 0.9–14.8) respectively in all eligible patients, the recruited and the non-recruited patients.

Conclusion: Selective recruitment resulted in an overestimation of POC CRP test use and antibiotic prescribing.

Introduction

Recruitment bias is a systematic error that can affect the validity of a study. Failure to recruit all eligible study patients is common,[1–4] but recruitment selection does not necessarily lead to a biased estimate of the study outcome. To evaluate selection in recruitment and possible bias, recruited patients should be compared to the total group of eligible patients. If these groups differ too much in baseline characteristics and studied associations, recruitment bias is likely, and this should be taken into account when interpreting the results. Many studies have reported on statistical solutions to adjust for recruitment bias in non-randomized therapeutic interventions that are widely embedded in daily care, such as influenza vaccination.[5–8] However, little is known about recruitment bias in studies on implementation of new interventions.
We recently completed a study on the impact of the implementation of C-reactive protein (CRP) point-of-care (POC) testing on antibiotic prescribing for acute cough patients in primary care in the Netherlands.[9] CRP is an inflammation marker, which is increasingly being measured in primary care at the point-of-care, i.e. during consultation. General practitioners (GPs) to help assess the severity of lower respiratory tract infection (LRTI) merely aiming to result in better antibiotic stewardship in patients presenting with acute cough use CRP. We found that the POC CRP test results changed the decision of GPs about antibiotic prescribing in patients with acute cough. However, it did not reduce overall antibiotic prescribing.[10] Of the included study patients, 78% were tested for POC CRP, which was higher than expected since POC CRP testing is only indicated in patients with diagnostic doubt on the diagnosis community-acquired pneumonia. Because of suspected selection bias, we conducted an analysis on the recruitment of patients. Our aim was to estimate the impact of selective patient inclusion on the results of the original study.

METHODS

Design

Observational study using data from a previously performed cross-sectional non-randomized implementation study and newly gathered data.[11]

Ethics

The act on medical research involving human subjects does not apply to this study and therefore an official approval of this study by the Medical Ethics Research Committee of the University Medical Center Utrecht was not required.

Setting and study population

Data of the original implementation study were collected from February 2012 to February 2013 in nine healthcare centres in the Netherlands. Participating GPs were instructed to recruit all consecutive adult patients presenting with acute or newly presented cough (defined as cough less than 24 days) during day care consulting hours. They reported their management (i.e. whether they ordered POC CRP testing or not) and their intention to prescribe antibiotics both before and after POC CRP testing on a case report form. All patients received ‘usual care’, i.e. the GPs independently decided on the diagnostic work-up (including use of POC CRP test) and management. Additionally, we collected usual care data retrospectively from March to September 2012 from four of the nine participating healthcare centres who participated in the implementation study. These four centres are academic primary healthcare centres participating in the Utrecht Primary Care Network. In these centres, routine care data can easily be extracted from the research database, which was the main reason for their selection. In these four centres, 20 GPs serve approximately 35 000 patients.[12]

Measurements

We, retrospectively, identified anonymised data of all potentially eligible patients that consulted the GPs between March to September 2012 from their electronic medical records (EMR), using International Classification of Primary Care (ICPC) codes[13]: R05 (cough), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), R74 (acute upper respiratory tract infection), R95 (COPD/emphysema), and R96 (asthma). In the case of ICPC codes R74, R95 or R96, we analysed the full EMR consultation texts and only included subjects if the consultation represented acute or newly presented cough (defined as cough less than 24 days). Patients that were included in the study by the GPs were labelled as ‘recruited patients’. For all patients the following data was extracted from their EMR: age, gender, relevant comorbidity—defined by ICPC code R95 (COPD), R96 (asthma), K77 (heart failure), and T90 (diabetes mellitus)—results of the infection parameters CRP,[14] erythrocyte sedimentation rate (ESR), and leukocyte count (LC), referral to the pulmonologist and the prescription of antibiotics by the GP within the four weeks after consultation. The latter was extracted from the EMRs using the Anatomical Therapeutic Chemical (ATC) classification code[15]: J01A (tetracyclines), J01C (beta-lactam antibacterials and penicillins) and J01F (macrolides, lincosamides and streptogramins). CRP level was dichotomized into <20 mg/l (low) and ≥20 mg/l (high), in concordance with the guidelines, which recommend to withhold antibiotics in patients with CRP <20 mg/l.[16,17] CRP results were from POC or central lab measurements, but we have no data on which method was used in how many patients. The validity of these methods is, however, comparable.

To evaluate possible mechanisms for selective recruitment all participating GPs that worked in the four academic primary healthcare centres completed a questionnaire enquiring about their main reasons...
not to have included all eligible patients, after data-
collection of the original study was completed.

Outcomes

The primary outcome was the size of selection, reflected by proportion of all eligible patients who
were included in the implementation study. Secondary
outcomes were the proportion of patients who under-
went POC CRP measurement, the proportion of
patients who were prescribed antibiotics and the
association between POC CRP level and antibiotic
prescribing.

Data analysis

To evaluate selective recruitment and subsequent bias,
we first compared the actual recruited patients with all
potentially eligible patients to determine the represen-
tativeness of the recruited subjects for the whole
group of eligible patients. Because the recruited
patients are a subgroup of all eligible patients, these
groups partly overlap. Therefore, a direct comparison
of these groups with formal statistical testing was not
applicable; hence, we consecutively tested for differen-
ces between recruited with non-recruited patients.

Distributions of patient characteristics (age, gender,
relevant comorbidity) and diagnostic and therapeutic
management (blood tests, antibiotic prescription, and
referral to pulmonologists) were computed for all eli-
gible patients, the recruited and the non-recruited
patients, and compared between the recruited and the
non-recruited patients. Means of continuous variables
and proportions for categorical variables were com-
pared using 95% confidence intervals (CIs). The distri-
bution of the continuous variables was checked for
linearity with the Levene’s test for equality, which
showed normal distribution, therefore the mean (with
standard deviation) was considered the most appropri-
ate summary measure.

Furthermore, the proportion and accompanying
95% CIs of being POC CRP tested and of receiving anti-
biotics were calculated and reported (without formal
statistical testing) for all eligible patients and the
recruited patients, and compared between recruited
and non-recruited with a P-value of 0.05 used as sig-
nificance level using chi-square tests.

To indicate how recruitment might have influenced
the results, the association between CRP level (dicho-
tomized at 20 mg/l) and antibiotic prescribing was
expressed as univariate odds ratio (OR) with accompa-
nying 95% CIs. First, we computed this association for
the three groups separately. Then, we compared the
ORs between recruited and non-recruited patients,
using the log likelihood ratio test ($\chi^2$ test) for the
differences between models with and without an inter-
action term for groups (recruited versus non-recruited).
We used this interaction term to estimate whether the
association between CRP results and antibiotic pre-
scribing (yes or no) differed between recruited and
non-recruited patients. Responses to the questionnaire
were summarized. Data were analysed using SPSS for
Windows 20.0.0 (SPSS, Inc. Chicago, Illinois, USA).

Results

During the study period, 1473 patients were eligible.
Three hundred and forty-eight (24%) had been
recruited by the 20 participating GPs of the four
centres. Table 1 shows patient characteristics of all eli-
gible patients, and of recruited and non-recruited
patients. These patient groups did not differ in age,
gender, the number of relevant comorbidities (heart

Table 1. Characteristics of all eligible patients, divided into recruited and non-recruited patients. Because the recruited patients and non-recruited patients together form the group of all eligible patients, formal statistical testing was not applicable to compare all eligible patients with the (non)-recruited patients.

| Characteristic                        | All eligible patients n = 1473 | Recruited patients n = 348 | Non-recruited patients n = 1125 | P-value\(^a\) |
|--------------------------------------|-------------------------------|----------------------------|-------------------------------|-------------|
| Mean age, years (SD, 95% CI)         | 48 (16, 47–49)                | 48 (15, 46–49)             | 48 (16, 47–49)                | 0.76        |
| Male gender, n (%, 95% CI)           | 607 (41, 39–44)               | 131 (38, 33–43)            | 476 (42, 40–45)               | 0.12        |
| Comorbidity                          |                               |                            |                               |             |
| Heart failure, n (%, 95% CI)          | 32 (2, 2–3)                   | 25 (2, 2–3)                | 0.81                          |
| COPD, n (%, 95% CI)                  | 103 (7, 6–8)                  | 75 (7, 5–8)                | 0.38                          |
| Asthma, n (%, 95% CI)                | 204 (14,12–16)                | 150 (13, 12–16)            | 0.30                          |
| Diabetes Mellitus, n (%, 95% CI)     | 132 (9, 8–11)                 | 103 (9,8–11)               | 0.64                          |
| Blood tests performed                |                               |                            |                               |             |
| CRP, n (%, 95% CI)                   | 342 (23, 21–25)               | 280 (81, 76–84)            | 62 (6, 4–7)                   | 0.00        |
| ESR, n (%, 95% CI)                   | 63 (4, 3–6)                   | 56 (5, 4–6)                | 0.02                          |
| LC, n (%, 95% CI)                    | 70 (5, 4–6)                   | 62 (6, 4–7)                | 0.01                          |
| Antibiotic prescription, n\(^a\) (%, 95% CI) | 477 (32, 30–35)            | 325 (29, 26–32)            | 0.00                          |
| Referral to pulmonologists, n\(^a\) (%, 95% CI) | 44 (3, 2–4)               | 29 (3, 2–4)                | 0.10                          |

SD, standard deviation; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LC, leucocyte count.
\(^a\)During 28 days of follow up.
\(^b\)The P-value accompanies the comparison of recruited versus non-recruited patients.
failure, COPD, asthma, and diabetes mellitus) and referrals to the pulmonologist.

In 342 (23%, 95% CI: 21–25) of all eligible patients, POC CRP test results were available. Two hundred and eighty (81%, 95% CI: 76–84) recruited patients had POC CRP test results, versus 62 (6%, 95% CI: 4–7) non-recruited patients ($P < 0.00$).

Of all eligible patients, 477 (32%, 95% CI: 30–35) received an antibiotic prescription. One hundred and forty-two (41.5%) recruited patients had POC CRP test results versus 68 (24.4%) non-recruited patients ($P < 0.00$), Table 1).

The OR for the association between CRP level and antibiotic prescribing was 18.2 (95% CI: 9.6–34.3) for all eligible patients, the recruited and the non-recruited patients, respectively (Table 2). The OR of the recruited and non-recruited patients differed significantly ($P$-value <0.01).

In total, 15 (75%) GPs completed the questionnaire. They reported as main reason for not having included all eligible patients that they frequently forgot to recruit eligible patients due to limited time per consultation. Questionnaire responses are summarized in Table 3.

**Table 2.** Antibiotic prescribing in point-of-care C-reactive protein (CRP) tested patients related to CRP level, in all eligible, recruited and non-recruited patients.

| CRP (mg/l) | Total n (%) | Antibiotics prescribed | No antibiotics prescribed | Total |
|------------|-------------|------------------------|--------------------------|-------|
| $\geq 20$ | 142 (41.5%) | 82 (85.4%) | 14 (14.6%) | 96 (100%) |
| $< 20$ | 200 (58.5%) | 60 (24.4%) | 186 (75.6%) | 246 (100%) |
| Total | 342 (100%) | 142 (41.5%) | 200 (58.5%) | 342 (100%) |

**Table 3.** Results from questionnaires completed by participating general practitioners to evaluate possible mechanisms for selection in recruitment.

| Information on participating general practitioners, n = 15 |
|-----------------------------------------------------------|
| Age, mean (SD)$^a$ | 38 (8) |
| Male, n | 1 |
| PhD, n | 3 |
| Years of experience as general practitioner, mean (range) | 7 (0–22) |
| POC CRP used for other diseases (non-LRTI), n$^b$ | 6 |
| Percentage included patients according to GP's, % | 89 |
| Information on study | Presentation, n | 3 |
| | Newsletter, n | 7 |
| | Poster, n | 1 |
| | Colleague, n | 10 |
| No information, n | 1 |
| Provided information was sufficient, n | 15 |
| Opinions of participating GPs | 0 = disagree, 7 = agree | (median score with range 0–7) |
| Did not encounter eligible patients | 1 |
| Forget to recruit due to busy schedule | 5 |
| No cooperation of patient | 1 |
| More information needed during recruitment timeframe | 2 |
| POC CRP is easy to perform$^c$ | 6 |
| Enough reminders provided during recruitment timeframe | 6 |

$^a$Missing data n = 1.
$^b$Missing data n = 2.
$^c$Missing data n = 6.

Indicated reason for the low recruitment rate. Confounding by (test) indication could be an explanation for a higher proportion of POC CRP testing and antibiotic prescribing in recruited subjects, assuming that GPs recruited predominantly patients for whom they were planning on POC CRP testing and/or prescribing antibiotics. A more active treatment attitude in recruited patients has been described previously by Grobbee et al.[18] A proactive treatment attitude concerning patients for whom the GP was already planning to prescribe antibiotics could have led to a more active filling out of registration forms. Misinterpretation of the study protocol, i.e. only including patients when CRP testing was considered, could also explain selection and bias. One could also argue that patients in the recruited group had more severe symptoms, which could explain why they were prescribed more antibiotics as compared to all eligible patients. Another explanation for the observed selection could be lack of knowledge of the study, which we conclude from the fact that 10 of 15 GPs (67%) heard about the study from a colleague. As most of the GPs work part-time,

**Discussion**

**Main findings**

In our study on implementation of POC CRP tests in adults presenting with acute cough in primary care, participating GPs recruited only 24% of all eligible patients. In recruited patients, POC CRP tests were conducted more frequently and antibiotics were prescribed more often than in non-recruited patients (81% versus 6% and 44% versus 29%, respectively). The magnitude of the positive association between CRP level and antibiotic prescribing was different for recruited and non-recruited patients.

**Interpretation of findings**

Forgetting to recruit patients due to time constraints as indicated by the participating GPs is the most
they could have been absent from study information meetings. Although these possible sources of selection are speculative, we think that the key source of bias was the fact that the GPs filled out registration forms when they were planning on POC CRP. This explains why most patients who presented with acute cough were tested and also the minority of eligible patients were included in the study. The results of this study underline the importance of analysis of recruitment (both recruited and non-recruited subjects) even in pragmatic observational studies.

**Strengths and limitations**

To the best of our knowledge, this is the first study that evaluated recruitment in an observational study on implementation of a diagnostic device in routine primary care. Some aspects should be considered when interpreting the results. First, because we conducted a retrospective study, retrieval of all information on signs and symptoms and their impact on recruitment was not possible. Nevertheless, we think that missing data because of insufficient registration was limited because the participating GPs have been well trained to record data in a standardized manner. Second, we chose to compare the actually recruited patients with all eligible patients, although this does not meet requirements for formal statistical testing because these groups partly overlap. We did this, because we aimed to assess the representativeness of the recruited group for all eligible patients. Third, it was not possible to detect the indication for all antibiotics prescribed. Antibiotics may have been prescribed for other diseases than lower respiratory tract infections. However, since we used ATC codes corresponding to the index consultation (i.e. linked to the ICPC codes) the risk of misinterpretation of antibiotic prescribing was small. Finally, the questionnaire was completed retrospectively, which may have induced recall bias.

**Comparison with literature**

Suboptimal recruitment caused by physician related factors—such as time constraints and forgetting to recruit as suggested by the questionnaires in the present study—has been reported before.[19] Under-recruitment is also problematic in randomized controlled trials (RCTs); in the UK less than one-third of the trials recruited to target and some trials were even forced to stop due to under-recruitment.[20–22] RCTs, in which patient informed consent is required, reported inclusion rates ranging from 38% to 61%.[1,4,23] Despite randomization, patient characteristics often differ between the study arms of a RCT and there is debate on whether statistical testing for baseline imbalances is appropriate to detect possible recruitment bias in trials and whether statistical techniques should be used to adjust for these imbalances.[24,25] Our study was not designed as a RCT and patients’ informed consent was not requested, which eliminates potential for consent bias.

Previous observational studies on non-randomized interventions, for example influenza vaccination,[7] have shown relevant bias regarding the preferences in patients receiving the interventions, where patients with worse prognosis were more likely to receive the intervention (confounding by indication).[5,7,8]

**Conclusion**

In a POC CRP implementation study, GPs recruited only a minority of eligible patients, which resulted in an overestimation of POC CRP testing, and antibiotic prescribing in recruited patients. Furthermore, the magnitude of the positive association between CRP level and antibiotic prescribing was different in both groups.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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