Cancer Epidemiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: A cohort study

Esben Næser[a,b,c,*], Ulrich Fredberg[c], Henrik Møller[a,b,d], Peter Vedsted[a,b,c]

[a] Research Unit for General Practice, Department of Public Health, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
[b] Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
[c] Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Falkevej 1-3, 8600 Silkeborg, Denmark
[d] Cancer Epidemiology and Population Health, King's College London, Great Maze Pond, London SE1 9RT, United Kingdom

ARTICLE INFO

Article history:
Received 7 June 2017
Received in revised form 26 July 2017
Accepted 27 July 2017
Available online xxx

Keywords:
Early cancer diagnosis
Neoplasm
Urgent referral
Denmark
General practice

ABSTRACT

Background: Little is known about the clinical characteristics of patients referred to a diagnostic centre through the Danish urgent referral pathway for non-specific serious symptoms. We aimed at estimating the distribution of serious disease and the diagnostic value of clinical characteristics for the diagnosis of cancer and serious non-malignant disease in these patients.
Method: A cohort study of 938 patients referred by their GP to the diagnostic centre at Silkeborg Regional Hospital. All patients were followed up for three months in national registries. The likelihood ratio (LR) of cancer or serious non-malignant disease were calculated in relation to clinical characteristics.
Results: A total of 327 (34.9%) patients were diagnosed with new serious disease within three months: 118 patients (12.6%) with malignant disease and 209 patients (22.3%) with non-malignant disease. Most patients presented general symptoms. The highest LR of cancer was found for abdominal mass, high lactate dehydrogenase or abnormal findings in the diagnostic imaging. The highest LR of non-malignant disease was found for swollen joints or abnormal auscultation of lung or chest.
Conclusions: Patients referred by their GP to the diagnostic centre have high risk of serious disease. A multidisciplinary diagnostic approach is needed to embrace the diagnostic spectrum.

1. Introduction

An urgent referral pathway for non-specific serious symptoms was implemented in Denmark in 2011–2012 [1]. This pathway was part of the Danish three-legged cancer strategy and supplemented the urgent referral pathways, which were based on alarm symptoms for specific cancer types [2]. The aim was to expedite cancer diagnosis by providing new referral possibilities from general practice for patients with non-specific symptoms that could be signs of serious disease [3].

The implementation was supported by studies demonstrating that the urgent referral pathways favoured patients presenting with specific alarm symptoms of cancer, whereas patients not presenting with these specific alarm symptoms had increased diagnostic intervals [4,5]. A Danish study among general practitioners (GPs) showed that half of cancer patients presented with symptoms that could not be categorised as alarm symptoms at first presentation; they presented with either non-specific serious symptoms (20%) or vague symptoms (30%) [4].

To prevent long-lasting fragmented diagnostic pathways, the urgent pathway for non-specific serious symptoms was designed as a two-step approach [3]. First, the GP initiates the diagnostic workup on the basis of the imaging results and a standardised panel of blood tests ("triage function"). Second, if relevant, the patient is referred to the diagnostic centre, where a multidisciplinary team takes over the responsibility for the patient [6].

Non-specific symptoms do not have an obvious link to one certain disease type or organ system. Therefore, the referral criteria in the urgent referral pathway for non-specific serious symptoms are less definitive than the symptoms in the pathways for specific cancer types [1]. Thus, little is known about the clinical characteristics of patients referred to the diagnostic centre from the GP or about the diagnostic spectrum of serious disease and the role of the clinical characteristics in the diagnosis of serious disease among referred patients.

The aim of this study was to estimate the distribution of serious disease (cancer and serious non-malignant disease) and to describe and quantify the diagnostic value of the clinical

Abbreviation: DCR, Danish Cancer Registry; GP, general practitioner; NPR, National Patient Registry.

* Corresponding author at: Research Unit for General Practice, Department of Public Health, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark.
E-mail address: esben.naeser@feap.dk (E. Næser).

http://dx.doi.org/10.1016/j.canep.2017.07.014
1877-7821/

characteristics for the diagnosis of serious disease among patients referred by their GP to the diagnostic centre at Silkeborg Regional Hospital.

2. Material and methods

2.1. Study design

A prospective cohort study of patients aged 18 years or more referred by their GP to the diagnostic centre at Silkeborg Regional Hospital through the urgent referral pathway for non-specific serious symptoms between 1 July 2012 and 30 September 2014. Patients were followed up for three months in national registries for the diagnosis of new serious disease (cancer or serious non-malignant disease). We excluded patients referred to the diagnostic centre from a hospital department and patients who declined complete diagnostic workup.

2.2. Setting and organisation of diagnostic pathway

All Danish residents have free access to diagnostic services and treatment through the publicly funded health-care system. The Danish medical services are divided into five regions, and each of these regions has at least one diagnostic centre. Approximately 21 diagnostic centres have now been established in Denmark. Silkeborg Regional Hospital is situated in the Central Denmark Region, and the diagnostic centre has a catchment area of approx. 177,000 residents aged 18 years or older.

The triage function at Silkeborg Regional Hospital consists of imaging and a standardized blood test panel. The imaging includes a combined thoracic X-ray and ultrasound of the upper and lower abdomen. A CT scan of chest, abdomen and pelvis is performed if considered relevant by the radiologist. The results of the investigations are returned to the GP within three working days. The GP decides on further diagnostic steps within eight working days. If the triage function yields no obvious explanation for the patient's symptoms, the GP is advised to refer the patient to the diagnostic centre.

The diagnostic centre is run by specialists in internal medicine. All patients are assigned a personal coordinator during the diagnostic workup; the coordinator schedules visits for diagnostic investigations and keeps track of the outpatient diagnostic trajectory.

The first visit to the diagnostic centre is scheduled within 1–3 days after referral. Based on the medical history and the results of investigations, patients undergo individual diagnostic programmes; these are developed in a close cooperation between relevant experts, and all medical specialties are represented in the diagnostic centre. Furthermore, the diagnostic centre has made preferential arrangements with specialists to hasten the diagnostic investigations (e.g. gynaecological examination, endoscopy, diagnostic imaging and biopsy). The programme may include concurrent workup in different medical specialties (e.g. gastroenterology and gynaecology), and these are coordinated in the diagnostic centre. All medical specialties are available for consulting on daily multidisciplinary conferences. The diagnostic centre is responsible for the patient during the entire diagnostic workup, which must be completed within 16 calendar days.

Table 1
Characteristics of patients investigated at the diagnostic centre (n = 938).

Variable	Number of patients (%)	
Gender		
Female	516	(55.0%)
Male	422	(45.0%)
Age group (yrs)		
18–39	47	(5.0%)
40–59	243	(25.9%)
60–79	546	(58.2%)
>80	102	(10.9%)
WHO performance status[a]		
0	588	(65.9%)
1	198	(22.2%)
≥2	107	(12.0%)
Chronic diseases prior to referral[a]		
0	456	(51.1%)
1	142	(15.9%)
2	140	(15.7%)
≥3	155	(17.4%)
Type of chronic disease[a]		
Hypertension	208	(23.3%)
Osteoarthritis or inflammatory arthritis	110	(12.3%)
Earlier cancer (besides non melanoma skin cancer)	98	(11.0%)
Chronic obstructive lung disease	96	(10.8%)
Diabetes	82	(9.2%)
Ischemic heart disease	72	(8.1%)
Mental illness[b]	65	(7.3%)
Stroke	55	(6.2%)
Osteoporosis	49	(5.5%)
Smoking[a]		
Current smoker	263	(29.4%)
Former smoker/intermittent smoking	288	(32.3%)
Never smoked	342	(38.3%)
Drinking habits[a]		
Daily drinking	173	(19.4%)
No daily drinking	720	(80.6%)

[a] 893 number of valid responses.
[b] 41 patients had mild to medium mental illness, and 24 had moderate to severe mental illness.

2.3. Data

Eligible patients were included from a clinical database at the diagnostic centre at Silkeborg Regional Hospital. The data were consecutively recorded for each patient by the involved healthcare personal. We assigned the index date as the date of first visit at the diagnostic centre. The unique civil registration number assigned to all Danish residents at birth or immigration allowed linkage to national registries [7]. The clinical laboratory information system (LABKA) was used to retrieve information on results of blood tests performed within 14 days from the index date [8]. Included blood tests were part of the standardized blood test panel performed in the triage function, and test results were identified by unique codes in LABKA [9].

Patients were followed up for three months after index date for diagnosis of cancer in the Danish Cancer Registry (DCR) [10]. Patients with no registered malignant diagnosis in the DCR were followed up in the National Patient Registry (NPR) for a non-malignant diagnosis [11]. Both registries were coded using the International Classification of Diseases, 10th edition (ICD-10). For each person, only the incident diagnosis was included; diagnoses registered within the ten years preceding the index date were excluded. Three authors (EN, UF and PV) reviewed all diagnoses and dichotomised into: 1) serious disease or 2) not serious disease. Disagreements were discussed until consensus was reached.

2.4. Variables

Symptoms were defined as presence or absence of 21 specified symptoms at the first visit to the diagnostic centre. Clinical findings were defined as findings by the physician during the clinical

Please cite this article in press as: E. Næser, et al., Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: A cohort study, Cancer Epidemiology (2017), http://dx.doi.org/10.1016/j.canep.2017.07.014