

Clinical characterisation of patients diagnosed with cancer following emergency self-referral

Xavier Bosch^{a,*}, Elisabet Montori-Palacin^a, Tiago Mota Gomes^b, José Naval-Álvarez^a, Pedro Moreno^a, Alfonso López-Soto^a

^a Department of Internal Medicine, Hospital Clínic, University of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS) and Clínic Foundation for Biomedical Research (FCRB), Villarroel 170, Barcelona 08036-Spain

^b Primary Care Centre Casanova, CAPSBE, Barcelona, Spain

ARTICLE INFO

Keywords:

Cancer diagnosis
Emergency self-referral
Emergency referral from primary care
Presenting symptoms
Diagnostic interval

ABSTRACT

Background: Despite their frequency and potential impact on prognosis, cancers diagnosed via self-referral to the emergency department are poorly documented. We conducted a detailed analysis of cancer patients diagnosed following emergency self-referral and compared them with those diagnosed following emergency referral from primary care. Given the challenges associated with measuring intervals in the emergency self-referral pathway, we also aimed to provide a definition of the diagnostic interval for these cancers.

Methods: A retrospective observational analysis was performed on patients diagnosed with 13 cancers, either following emergency self-referral or emergency referral from primary care. We analysed demographics, tumour stage, clinical data (including 28 presenting symptoms categorised by body systems), and diagnostic intervals by cancer site, then testing for differences between pathways.

Results: Out of 3624 patients, 37 % were diagnosed following emergency self-referral and 63 % via emergency referral from primary care. Emergency self-referrals were associated with a higher likelihood of being diagnosed with cancers manifesting with localising symptoms (e.g., breast and endometrial cancer), whereas the likelihood of being diagnosed with cancers featuring nonspecific symptoms and abdominal pain (e.g., pancreatic and ovarian cancer) was higher among patients referred from primary care. Diagnostic intervals in self-referred patients were half as long as those in patients referred from primary care, with most significant differences for pancreatic cancer (28 [95 % CI −34 to −23] days shorter, respectively).

Conclusion: These findings enrich the best available evidence on cancer diagnosis through emergency self-referral and showed that, compared with the emergency referral pathway from primary care, these patients had a significantly increased likelihood of presenting with symptoms that are strongly predictive of cancer. Since the starting point for the diagnostic interval in these patients is their emergency presentation, comparing it with that of those referred from primary care as an emergency is likely to result in biased data.

1. Background

Data from a recent study conducted in six high-income countries with public health systems revealed that, among 857,000 patients with eight common cancers, an average of 32 % (range 24–42.5 %) were diagnosed following emergency presentation (i.e., diagnosis of cancer within 30 days after an emergency hospital admission), with pancreatic and liver cancer displaying the highest proportions (average overall 46.1 and 40 %, respectively) [1]. Considering that emergency diagnosis of cancer is highly predictive of short-term mortality [1–4], reducing its

frequency is a top priority for healthcare systems [5].

When considering strategies to minimise the number of emergency cancer diagnoses, experts recommended factoring in patients' previous interactions with primary care [5]. Reports from the UK have shown that approximately two-thirds of patients with an emergency diagnosis have previously sought help from primary care, while the remaining third have not sought any at all [6–8]. Despite the wealth of information on patients with at least one and, more notably, three or more consultations before emergency referral [7,8], the population of cancer patients with no prior consultations who are diagnosed following self-referral to the

* Corresponding author.

E-mail address: xavbosch@clinic.cat (X. Bosch).

<https://doi.org/10.1016/j.canep.2024.102609>

Received 12 February 2024; Received in revised form 10 June 2024; Accepted 2 July 2024

Available online 9 July 2024

1877-7821/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

emergency department (herein referred to as ‘emergency self-referral’ [ESR]) is relatively unknown. Yet, this group holds potential implications for prognosis. Research by Murchie et al. demonstrated that not having prior contact with primary care was a powerful independent predictor of cancer diagnosis through emergency presentation [8].

Both route to diagnosis and intervals from first symptom to diagnosis can impact patient survival, clinical stage, and experience of care [1–3, 9–11]. Early diagnosis studies suggest that delayed help-seeking and prolonged intervals from first presentation to primary care to diagnosis (i.e., the diagnostic interval) contribute to cancer progression and eventual presentation as an emergency [4,5,12]. Since help-seeking and diagnostic intervals can be influenced by different patients’ factors (e.g., symptom awareness or personal beliefs), physicians’ decision-making, and system-related factors, enacting proactive measures that specifically target them may effectively reduce the frequency of emergency presentations. In England, for instance, an increased use of two-week-wait referral pathways for suspected cancer by primary care physicians has been associated with a significant reduction in the number of emergency presentations [6,13]. Similarly, educational campaigns have changed the way people seek care and how primary care physicians refer patients [14,15].

Notwithstanding the adverse consequences of delayed diagnosis and diagnosis through emergency presentation, information on intervals for this route is limited. Although the publication of the Aarhus statement in 2012 marked a turning point in the global effort to expedite cancer diagnosis [16], its definitions of time points and intervals have been mostly used for cancers diagnosed through nonemergency routes from primary care to hospital. Although key intervals align well with the emergency referral pathway from primary care, measuring them for cancers diagnosed through the ESR pathway is challenging.

We conducted a detailed analysis of a large population of patients with cancer who were diagnosed following ESR and compared them with those diagnosed following emergency referral from primary care (ERPC). Additionally, we aimed to define time-related metrics for the ESR pathway.

2. Material and methods

2.1. Design and setting

We conducted a retrospective observational analysis of patients with an emergency diagnosis of cancer seen at Hospital Clínic of Barcelona. Eligible patients were identified by searching through the digital health records (DHRs) of the hospital and its associated primary care centres. With 820 adult beds and a catchment area consisting of 600,000 people, this public academic institution provides advanced medical care to patients referred from 14 primary care centres and patients attending the emergency department.

Typically, patients experiencing cancer symptoms seek care from a primary care physician before being referred to hospital for specialist assessment. Based on the urgency and severity of symptoms, some patients are referred to the emergency department, while others without prior contact with primary care opt to do so themselves. Upon reaching the emergency department, patients are cared for by emergency physicians and may subsequently be admitted to hospital or referred as outpatients to the cancer diagnostic centre for additional testing and diagnosis. Emergency physicians have at their disposal specific guidelines for referral to this centre [17].

2.2. Population and pathways to diagnosis

Patients aged 18 and older who were diagnosed with cancer, either following ESR or ERPC, between September 2016 and October 2023 were eligible. Emergency diagnosis of cancer was defined as diagnosis following presentation to the emergency department and hospital admission or diagnosis following presentation to the emergency

department and referral to the cancer diagnostic centre. Date of diagnosis was the date of cancer diagnosis documented in the pathology report. Cancers sites included lung, pancreatic, colorectal, gastric, oesophageal, head/neck squamous cell (HNSC) (oral cavity, oropharyngeal, hypopharyngeal, and laryngeal), ovarian, liver, breast, prostate, endometrial, kidney/bladder, and cervical cancer. These cancers accounted for 80.5 % of all newly diagnosed cases in Spain in 2022 (excluding non-melanoma skin cancer) and are characterised by varying degrees of aggressiveness [18].

We reviewed the primary care centres’ DHRs of patients with an emergency diagnosis of cancer to establish whether they had initially consulted with a primary care physician. The study population was then split into two separate pathways: ESR and ERPC pathways. While ESR patients had no history of previous contact with primary care, ERPC patients had consulted at least once. As previously suggested, for each ERPC patient, we assessed all primary care appointments up to 730 days before they were referred to the emergency department [19]. We determined the number of primary care consultations and categorised them as one, two, or three or more. With a reported frequency of one-third of emergency presentations and their association with unfavourable outcomes [7,8,20,21], cancer patients with three or more consultations (ERPC ≥ 3) were classified as a third group of interest.

Complete availability of study variables was required for inclusion. Patients who were not referred through the specified sources or pathways, those who did not meet the evaluation criteria of the diagnostic centre, and cancers diagnosed during the Covid-19-impacted period March 2020–September 2021 were excluded. Exclusion criteria also applied to cancers in asymptomatic individuals, discovered incidentally or through screening, and cancers without histopathological proof.

2.3. Data collection

We systematically compiled data from the hospital and primary care centres’ DHRs and added them to a deidentified database. The quality and reliability of the data were evaluated through external audits. Relevant information included gender (male, female); age at diagnosis (continuous variable and age groups); zip code-based income (€/year) (high, medium, low, very low); education (highest, medium-high, medium-low, lowest); ethnicity (white, other); previous malignancy and relapses at follow-up; comorbidities according to Charlson score (0, 1, 2, ≥ 3) [22]; smoking habit (former, active, never); alcohol usage (low, high, none); stage at diagnosis according to TNM Classification of Malignant Tumours (I–II, III–IV) [23]; and presenting symptoms. Information on symptoms experienced by patients within each group were elicited during prediagnosis encounters at the diagnostic centre or inpatient wards and also retrieved from the DHRs and referral forms. We assessed the nature, number, and date of onset of each presenting symptom. Examination of unstructured (free-text) medical data revealed 28 distinct symptoms. Symptom selection was mainly based on UK NICE guidelines (2015), which are organised by symptoms and primary care test results, and require urgent (i.e., two-week-wait) or immediate (i.e., emergency) referral for patients with symptoms with a positive predictive value for cancer ≥ 3 % [24]. Symptoms were categorized by body systems, as follows: (1) Gastrointestinal/digestive (abnormal oral exam findings [oral cavity lumps/ulcerations/patches, lip lumps], dyspepsia, reflux, nausea/vomiting, haematemesis, dysphagia, bowel habit change, rectal bleeding, abdominal pain, back pain, abdominal mass, ascites); (2) Respiratory (cough, hoarseness, dyspnoea, haemoptysis, chest pain); (3) Urinary (haematuria, dysuria, lower urinary tract symptoms, suspected prostate cancer on digital rectal examination); and (4) Reproductive (women) (vaginal bleeding, vaginal discharge). Additional categories included nonspecific symptoms (unintentional weight loss, appetite loss, fatigue, fever); breast lump/nipple changes; peripheral lymphadenopathy; iron-deficiency anaemia; and jaundice. Symptoms were assessed individually, without considering potential combinations.

We examined and recorded the length of the diagnostic interval and

its variation by cancer type in the three pathways. For ESR patients, the diagnostic interval was the time between date of ESR and date of diagnosis, while for ERPC and ERPC ≥ 3 patients, it was the time from primary care presentation to diagnosis. We also evaluated the total interval to diagnosis (i.e., from symptom onset to diagnosis following ESR or ERPC), which includes the patient interval (i.e., from symptom onset to date of ESR or primary care presentation) and the primary care interval (i.e., from date of primary care presentation to date of emergency referral). Interval definitions were consistent with Aarhus statement guidelines [16].

2.4. Statistical analyses

Differences in sociodemographic, clinical, and tumour variables were evaluated using *t*- or Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. For presenting symptoms, differences between ESR vs. ERPC and ERPC ≥ 3 patients were assessed with χ^2 tests, computing the odds ratios (with 95 % confidence intervals [CI]) of the differences between proportions. The length of intervals (in days) was analysed overall and for each cancer type, and values are reported as the median, interquartile range (IQR), 90th centile, and range. Differences between populations were examined with Kruskal-Wallis nonparametric analysis of variance, Dunn's, and Wilcoxon rank-sum tests. The effect size between groups was determined using the Hodges-Lehmann nonparametric test, and the medians of the differences between each value (including 95 % CI for differences) are reported [25,26]. Data analysis was performed using the statistical package OriginPro 2022 (OriginLab, Northampton, MA, USA) and significance was set at 0.05 α level. Graphics were generated with GraphPad Prism v10 (GraphPad Software, San Diego, CA, USA).

3. Results

Out of 3873 patients, 249 (6.4 %) were excluded and 3624 were selected for final analysis. Of these, 1349 (37.2 %) were classified as ESR and 2275 (62.8 %) as ERPC patients. Among the 2275 ERPC patients, 1225 (33.8 % of the total) made the ERPC ≥ 3 group (Fig. S1).

3.1. Cancer diagnoses and clinical stage

Overall, pancreatic, colorectal, and lung cancer were the most frequent diagnoses in the study, accounting for 14.1, 13.4, and 13.1 % of 3624 cancers, respectively, whereas, cervical, endometrial, and HNSC cancer were the least common (2.3, 3.9, and 4.6 % of all cancers, respectively). By pathways, ERPC and ERPC ≥ 3 patients were significantly more likely than ESR patients to be diagnosed with pancreatic

(15.6 % of 2275 ERPC and 17.5 % of 1225 ERPC ≥ 3 cancers vs. 11.6 % of 1349 ESR cancers; $P = 0.0009$ and < 0.0001 on χ^2 tests, respectively) and ovarian cancer (8.4 and 9.3 % of ERPC and ERPC ≥ 3 cancers vs. 6 % of ESR cancers; $P = 0.0083$ and 0.0016 , respectively). In addition, patients who self-referred directly as an emergency were significantly more likely than ERPC and ERPC ≥ 3 patients to be diagnosed with oesophageal, breast, endometrial, and kidney/bladder cancer. For example, oesophageal cancer accounted for 9.2 % of all cancers in ESR patients vs. 7.2 and 6.3 % in ERPC and ERPC ≥ 3 patients ($P = 0.033$ and 0.0061 , respectively) (Table 1).

As shown in Table S1, there were no significant differences in tumour stage between populations. Overall, 73.1, 74.9, and 76.8 % of ERPC, ESR, and ERPC ≥ 3 patients were diagnosed with stage III-IV cancers, respectively, with pancreatic, lung, and gastric cancer displaying the highest proportions of stage III-IV disease.

3.2. Patient characteristics

Characteristics of study patients are outlined in Table 2. No significant differences were found between ESR and ERPC patients in gender, age (67 [IQR 52–79] vs. 65 [50–80] years; $P = 0.194$ on Wilcoxon rank-sum test, respectively), income, education, ethnicity, and comorbidities. However, ESR patients were more likely to have an excessive alcohol consumption. Gender and age did not vary significantly between ESR and ERPC ≥ 3 patients, but the latter were more likely to belong to other ethnic groups and less likely to be active smokers and excessive alcohol drinkers.

3.3. Symptoms on presentation

Table 3 shows the frequency of presenting symptoms relative to all cancers in ESR, ERPC, and ERPC ≥ 3 groups and the odds ratios for differences between proportions for each symptom. Individual symptoms in this table are categorized as alarm and nonalarm symptoms. Most common symptoms were nonspecific symptoms, abdominal pain, and bowel habit change, accounting for 45.8, 59.5, and 66.3 % of cancers in ESR, ERPC, and ERPC ≥ 3 patients, respectively. Out of the 28 assessed symptoms, 19 were localising (i.e., alarm) in nature. Individually, ESR were significantly more likely than ERPC patients to present with alarm symptoms such as haematemesis, dysphagia, or haematuria and differences were even greater when compared with ERPC ≥ 3 patients. When considered in combination, alarm symptoms accounted for 76.8 % of ESR vs. 67.9 and 59.6 % of ERPC and ERPC ≥ 3 patients (odds ratio 1.56 [95 % CI 1.34–1.82] and 2.24 [95 % CI 1.89–2.66] on χ^2 tests, respectively; $P < 0.0001$). Conversely, ERPC and ERPC ≥ 3 were significantly more likely than ESR patients to experience nonspecific

Table 1

Distribution of emergency cancer diagnoses within study pathways and their frequency relative to the total number of cancers.

Cancer Type	Total (N = 3624)	ESR (n = 1349)	ERPC (n = 2275)	ERPC ≥ 3 (n = 1225)	ESR vs. ERPC P-value	ESR vs. ERPC ≥ 3 P-value
Lung	474 (13.1)	180 (13.3)	294 (12.9)	172 (14.0)		
Pancreatic	512 (14.1)	157 (11.6)	355 (15.6)	214 (17.5)	0.0009	< 0.0001
Colorectal	487 (13.4)	183 (13.6)	304 (13.4)	174 (14.2)		
Gastric	308 (8.5)	126 (9.3)	182 (8.0)	108 (8.8)		
Oesophageal	288 (7.9)	124 (9.2)	164 (7.2)	77 (6.3)	0.033	0.0061
HNSC	167 (4.6)	52 (3.9)	115 (5.1)	55 (4.5)		
Ovarian	272 (7.5)	81 (6.0)	191 (8.4)	114 (9.3)	0.0083	0.0016
Liver	251 (6.9)	80 (5.9)	171 (7.5)	84 (6.9)		
Breast	188 (5.2)	85 (6.3)	103 (4.5)	42 (3.4)	0.020	0.0008
Prostate	209 (5.8)	68 (5.0)	141 (6.2)	71 (5.8)		
Endometrial	141 (3.9)	76 (5.6)	65 (2.9)	23 (1.9)	< 0.0001	< 0.0001
Kidney/bladder	244 (6.7)	106 (7.9)	138 (6.1)	66 (5.4)	0.038	0.012
Cervical	83 (2.3)	31 (2.3)	52 (2.3)	25 (2.0)		

P values: Datasets were compared using χ^2 tests. Only statistically significant results are displayed. Abbreviations: ESR, emergency self-referral; ERPC, emergency referral from primary care; ERPC ≥ 3 , patients from the ERPC group who had three or more consultations; HNSC, head/neck squamous cell cancers.

Table 2
Characteristics of 3624 patients with an emergency diagnosis of cancer stratified by study groups.

Variable	ESR (n = 1349)	ERPC (n = 2275)	ERPC ≥ 3 (n = 1225)	ESR vs. ERPC P- value	ESR vs. ERPC ≥ 3 P-value
Gender, No. (%)				0.139	0.052
Females	631 (46.8)	1122 (49.3)	620 (50.6)		
Males	718 (53.2)	1153 (50.7)	605 (49.4)		
Age (years)				0.143	0.062
Mean (SD)	66.0 (15.6)	65.2 (17.3)	64.8 (18.1)		
Median (IQR)	67 (52–79)	65 (50–80)	65 (49–80)	0.194	0.093
Range (min–max)	40–92	33–95	33–95		
Age group, No. (%)					
≤ 40	0 (0.0)	159 (7.0)	113 (9.2)		
40–49	273 (20.2)	383 (16.8)	205 (16.7)		
50–59	237 (17.6)	370 (16.3)	192 (15.7)		
60–69	240 (17.8)	388 (17.1)	189 (15.4)		
70–79	262 (19.4)	388 (17.1)	204 (16.7)		
80–89	250 (18.5)	372 (16.4)	189 (15.4)		
≥ 90	87 (6.4)	215 (9.5)	133 (10.9)		
Income (€/year), No. (%)				0.122	0.805
High	22 (1.6)	55 (2.4)	25 (2.0)		
Medium	432 (32.0)	774 (34.0)	392 (32.0)		
Low	840 (62.3)	1373 (60.4)	764 (62.4)		
Very low	55 (4.1)	73 (3.2)	44 (3.6)		
Education, No. (%)				0.188	0.889
High	115 (8.5)	228 (10.0)	110 (9.0)		
Medium	386 (28.6)	694 (30.5)	363 (29.6)		
Low	513 (38.0)	830 (36.5)	458 (37.4)		
Very low	335 (24.8)	523 (23.0)	294 (24.0)		
Ethnicity, No. (%)				0.112	0.020
White	1275 (94.5)	2120 (93.2)	1130 (92.2)		
Other	74 (5.5)	155 (6.8)	95 (7.8)		
Previous malignancy, No. (%)					
Yes	83 (6.2)	125 (5.5)	64 (5.2)	0.410	0.311
Relapse	5 (6.0)	6 (4.8)	3 (4.7)		
Median follow-up (months) (IQR)	38 (32–45)	37 (29–46)	36 (30–43)		
Comorbidity burden, No. (%)				0.302	0.073
0	479 (35.5)	842 (37.0)	474 (38.7)		
1	407 (30.2)	719 (31.6)	381 (31.1)		
2	308 (22.8)	486 (21.4)	256 (20.9)		
≥ 3	155 (11.5)	228 (10.0)	110 (9.0)		
Smoking habit, No. (%)				0.053	0.031
Former	594 (44.0)	958 (42.1)	516 (42.1)		
Active	467 (34.6)	751 (33.0)	394 (32.2)		

Table 2 (continued)

Variable	ESR (n = 1349)	ERPC (n = 2275)	ERPC ≥ 3 (n = 1225)	ESR vs. ERPC P- value	ESR vs. ERPC ≥ 3 P-value
Never	288 (21.3)	566 (24.9)	315 (25.7)		
Alcohol usage, No. (%)				0.017	0.0054
Low	353 (26.2)	667 (29.3)	361 (29.5)		
High	131 (9.7)	170 (7.5)	80 (6.5)		
None	865 (64.1)	1438 (63.2)	784 (64.0)		

P values: Differences were analysed with χ^2 tests for categorical variables and *t*- or Wilcoxon rank-sum tests for continuous variables. Bold text is used to highlight statistically significant results. Abbreviations: ESR, emergency self-referral; ERPC, emergency referral from primary care; ERPC ≥ 3, patients from the ERPC group who had three or more consultations; SD, standard deviation; IQR, interquartile range.

symptoms (26.2 and 29.4 vs. 19.3 %; odds ratio 1.48 [95 % CI 1.26–1.75] and 1.74 [95 % CI 1.45–2.10], respectively; *P* < 0.0001) and abdominal pain (22.4 and 25.8 vs. 15.4 %; odds ratio 1.59 [95 % CI 1.33–1.89] and 1.91 [95 % CI 1.57–2.32], respectively; *P* < 0.0001). Overall, nonalarm symptoms accounted for 85.7 and 92.1 % of ERPC and ERPC ≥ 3 vs. 72.3 % of ESR patients (odds ratio 1.56 [95 % CI 1.34–1.82] and 2.24 [95 % CI 1.89–2.66], respectively; *P* < 0.0001).

3.4. Time intervals

The length of intervals varied largely by cancer type. Median diagnostic intervals were significantly shorter in ESR than in ERPC and ERPC ≥ 3 patients, both overall and for each cancer type. Overall, the diagnostic interval in ESR was 21 (13–31) days, while it was 40 (25–61) days in ERPC (difference –18 [95 % CI –19 to –17] days) and 50 (30–73) days in ERPC ≥ 3 patients (difference –27 [95 % CI –29 to –26] days) (Fig. 1). For pancreatic cancer, diagnostic intervals in ESR were 28 (95 % CI –33 to –20) days shorter than in ERPC patients, and, for gastric cancer, they were 27 (95 % CI –33 to –21) days shorter (Fig. 2, Table S2). There were even greater differences by cancer type when comparing ESR vs. ERPC ≥ 3 patients. For example, diagnostic intervals for pancreatic cancer in ESR patients were 43 (95 % CI –50 to –35) days shorter than in those from the ERPC ≥ 3 group (Table S3). Overall and by cancer type, the pattern of variation in the total interval to diagnosis was consistent with that observed for the diagnostic interval (Tables 4 and S4). Patient intervals in ESR were similar to those in ERPC patients, except for lung cancer (4 days shorter in ESR), and they were moderately shorter than in ERPC ≥ 3 patients, overall (4 [95 % CI –5 to –3] days shorter) and by cancer type, most notably for HNSC, lung, colorectal, and liver cancer (Tables S5 and S6).

4. Discussion

The results of this study amplify the current evidence on cancer diagnosis through the emergency self-referral pathway and show that these patients are more likely than those diagnosed through the emergency referral pathway from primary care to present with symptoms that are strongly predictive of cancer. In addition, analysis of intervals from symptom onset to diagnosis revealed that the diagnostic interval is in theory a suitable time metric for measuring the emergency self-referral pathway and that its length was half of that for the emergency referral pathway from primary care.

Out of all reported studies on emergency-diagnosed cancers, only three (Herbert et al., Abel et al., and Murchie et al.) have examined the subset of patients self-referring directly to the emergency department

Table 3

Number and frequency of individual symptoms relative to all cancers in each study population.

Presenting symptom	ESR (n = 1349)	ERPC (n = 2275)	ERPC ≥ 3 (n = 1225)	ESR vs. ERPC		ESR vs. ERPC ≥ 3	
				OR	P-value	OR	P-value
				[95 % CI]		[95 % CI]	
Alarm symptoms							
Total	1036 (76.8)	1545 (67.9)	730 (59.6)	1.56 [1.34,1.82]	< 0.0001	2.24 [1.89, 2.66]	< 0.0001
Abnormal oral findings	7 (0.5)	21 (0.9)	9 (0.7)	0.56 [0.23,1.26]	0.179	0.70 [0.27, 1.75]	0.487
Haematemesis	23 (1.7)	18 (0.8)	5 (0.4)	2.17 [1.19, 3.94]	0.012	4.23 [1.65, 10.27]	0.0015
Dysphagia	120 (8.9)	159 (7.0)	75 (6.1)	1.30 [1.02, 1.66]	0.037	1.50 [1.11, 2.03]	0.008
Rectal bleeding	54 (4.0)	72 (3.2)	33 (2.7)	1.28 [0.88, 1.84]	0.183	1.51 [0.97, 2.32]	0.066
Abdominal mass	124 (9.2)	225 (9.9)	124 (10.1)	0.92 [0.73, 1.16]	0.491	0.90 [0.69, 1.17]	0.424
Cough	75 (5.6)	117 (5.1)	58 (4.7)	1.09 [0.80, 1.46]	0.588	1.18 [0.83, 1.68]	0.345
Hoarseness	17 (1.3)	45 (2.0)	23 (1.9)	0.63 [0.35, 1.10]	0.107	0.67 [0.36, 1.23]	0.206
Dyspnoea	46 (3.4)	76 (3.3)	34 (2.8)	1.02 [0.71, 1.47]	0.911	1.24 [0.80, 1.93]	0.354
Haemoptysis	58 (4.3)	90 (4.0)	38 (3.1)	1.09 [0.78, 1.52]	0.614	1.40 [0.92, 2.10]	0.109
Chest pain	48 (3.6)	74 (3.3)	33 (2.7)	1.10 [0.75, 1.58]	0.622	1.33 [0.86, 2.08]	0.210
Haematuria	84 (6.2)	102 (4.5)	44 (3.6)	1.41 [1.06, 1.90]	0.022	1.78 [1.24, 2.57]	0.0021
Dysuria	22 (1.6)	24 (1.1)	9 (0.7)	1.55 [0.85, 2.79]	0.134	2.24 [1.04, 4.91]	0.037
Lower urinary tract symptoms	39 (2.9)	84 (3.7)	38 (3.1)	0.78 [0.53, 1.14]	0.198	0.93 [0.59, 1.48]	0.754
Suspected prostate cancer on DRE	28 (2.1)	60 (2.6)	27 (2.2)	0.78 [0.50, 1.23]	0.288	0.94 [0.55, 1.61]	0.822
Vaginal bleeding	88 (6.5)	95 (4.2)	35 (2.9)	1.60 [1.19, 2.16]	0.0018	2.37 [1.58, 3.53]	< 0.0001
Vaginal discharge	34 (2.5)	35 (1.5)	10 (0.8)	1.65 [1.02, 2.68]	0.037	3.14 [1.61, 6.44]	0.0009
Breast lump/nipple changes	68 (5.0)	77 (3.4)	27 (2.2)	1.52 [1.08, 2.11]	0.014	2.36 [1.51, 3.68]	0.0001
Iron-deficiency anaemia	86 (6.4)	122 (5.4)	73 (6.0)	1.20 [0.91, 1.59]	0.205	1.07 [0.78, 1.47]	0.662
Jaundice	15 (1.1)	49 (2.2)	35 (2.9)	0.51 [0.29, 0.91]	0.021	0.38 [0.20, 0.71]	0.0014
Nonalarm symptoms							
Total	975 (72.3)	1950 (85.7)	1128 (92.1)	0.43 [0.37, 0.51]	< 0.0001	0.23 [0.18, 0.29]	< 0.0001
Dyspepsia	73 (5.4)	90 (4.0)	46 (3.8)	1.39 [1.01, 1.89]	0.041	1.47 [1.01, 2.12]	0.0456
Reflux	31 (2.3)	46 (2.0)	24 (2.0)	1.14 [0.71, 1.80]	0.578	1.18 [0.70, 1.98]	0.553
Nausea/vomiting	69 (5.1)	88 (3.9)	41 (3.3)	1.34 [0.97, 1.85]	0.075	1.56 [1.05, 2.29]	0.027
Change in bowel habit	150 (11.1)	249 (10.9)	136 (11.1)	1.02 [0.82, 1.26]	0.871	1.00 [0.78, 1.28]	0.989
Abdominal pain	208 (15.4)	510 (22.4)	316 (25.8)	0.63 [0.53, 0.75]	< 0.0001	0.52 [0.43, 0.64]	< 0.0001
Ascites	81 (6.0)	152 (6.7)	87 (7.1)	0.89 [0.68, 1.17]	0.422	0.84 [0.61, 1.14]	0.260
Back pain	54 (4.0)	99 (4.4)	60 (4.9)	0.92 [0.66, 1.28]	0.614	0.81 [0.56, 1.17]	0.270
Nonspecific symptoms	260 (19.3)	595 (26.2)	360 (29.4)	0.67 [0.57, 0.79]	< 0.0001	0.57 [0.48, 0.69]	< 0.0001
Peripheral lymphadenopathy	49 (3.6)	121 (5.3)	58 (4.7)	0.67 [0.48, 0.94]	0.020	0.76 [0.52, 1.12]	0.162

P values: Datasets were compared using χ^2 tests. Odds ratios (95 % CI) of differences between proportions are shown. Abbreviations: ESR, emergency self-referral; ERPC, emergency referral from primary care; ERPC ≥ 3 , patients from the ERPC group who had three or more consultations; OR, odds ratio; CI, confidence interval; DRE, digital rectal examination.

[6–8]. However, there was no mention of presenting symptoms or stage at diagnosis in any of them. To better inform clinical practice, we explored the symptom signature of cancers (i.e., the nature and relative frequency of presenting symptoms) in each group and found a distinct symptom profile among affected individuals. Self-referred patients were

significantly more likely than those referred from primary care to report symptoms associated with high predictive values for cancer such as dysphagia, haematuria, or vaginal bleeding, whereas the latter were significantly more likely than the former to experience nonspecific symptoms and abdominal pain. As predicted by the nature of presenting

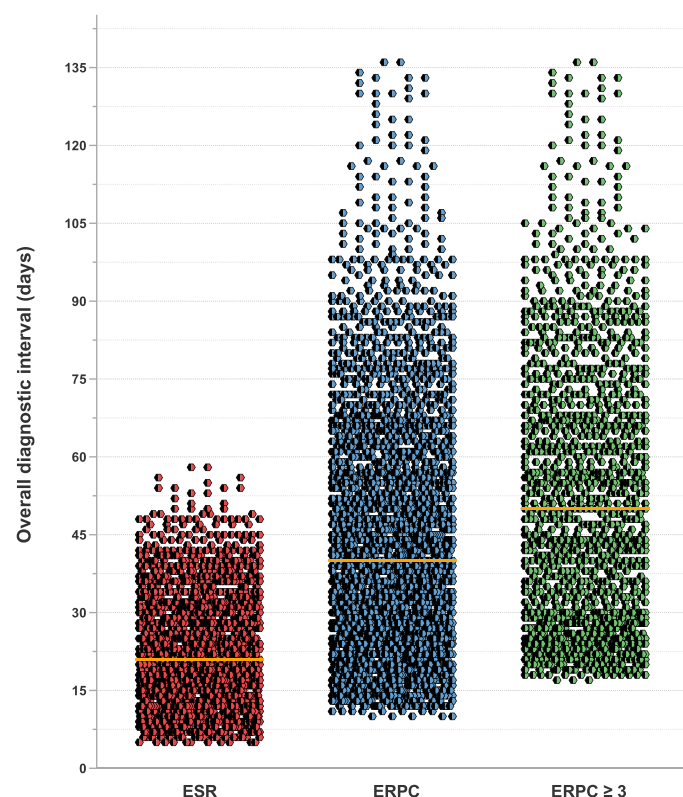


Fig. 1. Expanded scatter dot plots illustrating the overall diagnostic interval (in days) in patients with emergency-diagnosed cancers ($N = 3624$) according to study groups. Symbols represent the data points within each population, and the median is shown by a horizontal orange line. Abbreviations: ESR, emergency self-referral; ERPC, emergency referral from primary care; $ERPC \geq 3$, patients from the ERPC group who had three or more consultations.

symptoms, self-referred patients had significantly higher proportions of oesophageal, breast, endometrial, and kidney/bladder cancer diagnoses. These cancers are characterised by a narrow symptom signature, consisting of one symptom strongly associated with a specific cancer [27]. By contrast, patients referred from primary care were significantly more likely to be diagnosed with pancreatic and ovarian cancer. The symptomatic picture of these cancers includes vague or nonspecific symptoms and only one or two symptoms highly predictive of cancer (e.g., jaundice in pancreatic cancer) [27]. Interestingly, the distribution of cancer diagnoses and demographic profile of our population of self-referred patients share similarities with those reported by Abel et al. [7]. However, the lack of information on cancer symptoms limits comparability with our findings.

By defining time points and intervals in the emergency self-referral pathway, our investigation fills a gap in the literature and provides valuable data to inform future research. According to the Aarhus statement, the dates of first symptom, presentation, referral, and diagnosis are key markers in the patient journey to cancer diagnosis. It highlights the importance of identifying “where first presentation occurs (e.g., primary care, hospital department and so on)” and defining the referral date as “the time point at which there is a transfer of responsibility from one health-care provider to another for further clinical diagnostic and management activity” [16]. While the primary care interval is not suitable for use in the emergency self-referral pathway (i.e., no previous consultations), the diagnostic interval is effectively aligned when the dates of ‘first presentation’ and emergency presentation match up and the ‘referral’ date denotes the moment in which emergency physicians transfer responsibility to physicians at inpatient wards or the diagnostic centre.

4.1. Strength and limitations

Our study has several limitations. First, although data were collected from a high-volume academic medical institution in Barcelona, the research was limited by its single-site design, which restricts the generalisability of results to other populations. This limitation could be addressed through a larger multicentre investigation, comparing data from independent settings. Such investigation would have also the potential to enhance the quality of findings, leading to stronger conclusions. Second, patients with identical or similar symptoms but diagnosed with conditions other than cancer were not considered. Third, the process of eliciting and recording symptoms during clinical encounters, or retrieving them from primary care records, is prone to errors. However, the symptom signatures are consistent with those reported for the same cancer types. Last, we did not explore the wider context and motives that resulted in emergency self-referrals.

Notwithstanding its limitations, the study does have some strengths. We used a comprehensive dataset to characterise the clinical profile of self-referred patients, including their presenting symptoms, and to examine Aarhus-compliant intervals within this pathway. We also sought to mitigate potential biases arising from missing information by ensuring that study variables were fully available before inclusion.

4.2. Implications for research and clinical practice

The findings of this study have potential implications for public health practice and research. The patient case-mix of emergency self-referrals skewed towards alarm symptoms, suggesting opportunities for earlier presentation through public health education campaigns. This potential implication assumes that at least some patients would have been experiencing these symptoms for a considerably long time before their emergency presentation. Public campaigns to promote awareness of possible cancer symptoms have yielded promising results in England, with statistically significant increases in the number of primary care attendances and number of urgent referrals for suspected cancer [14].

The nature of presenting symptoms in cancer patients shapes the length of intervals from symptom onset to diagnosis. Although the distinctive symptom expression of cancers in the emergency self-referral pathway made them easier to suspect and diagnose, the key factor in determining the length of the diagnostic interval was the lack of utilisation of primary care services. Consequently, despite being methodologically sound, upcoming research should be aware of the potential for biased conclusions when evaluating differences in intervals between emergency pathways.

Considering the 37 % frequency of emergency cancer diagnoses and the potential impact on outcomes, understanding the reasons for emergency self-referral through qualitative research methods may uncover meaningful data that can inform the design and implementation of mitigating strategies. Lyratzopoulos et al. and Abel et al. have previously contended that a subset of these patients may have delayed elective care due to psychosocial factors such as symptom literacy, fear, or fatalism, choosing instead to self-refer to the emergency department, thus creating opportunities to decrease the number of such occurrences [5,7].

5. Conclusion

Timely identification of cancer symptoms facilitates diagnosis, but a lengthy diagnostic process and diagnosis through the emergency route can compromise prognosis. Our research provides a detailed clinical depiction of cancer patients diagnosed after self-referring to the emergency department. By comparing these patients with those diagnosed following emergency referral from primary care, we found that self-referred patients were more likely to be diagnosed with cancers characterised by localising or alarm symptoms and less likely to have cancers manifesting with nonlocalising symptoms and abdominal pain. By assessing intervals to diagnosis, we found that patients who sought help

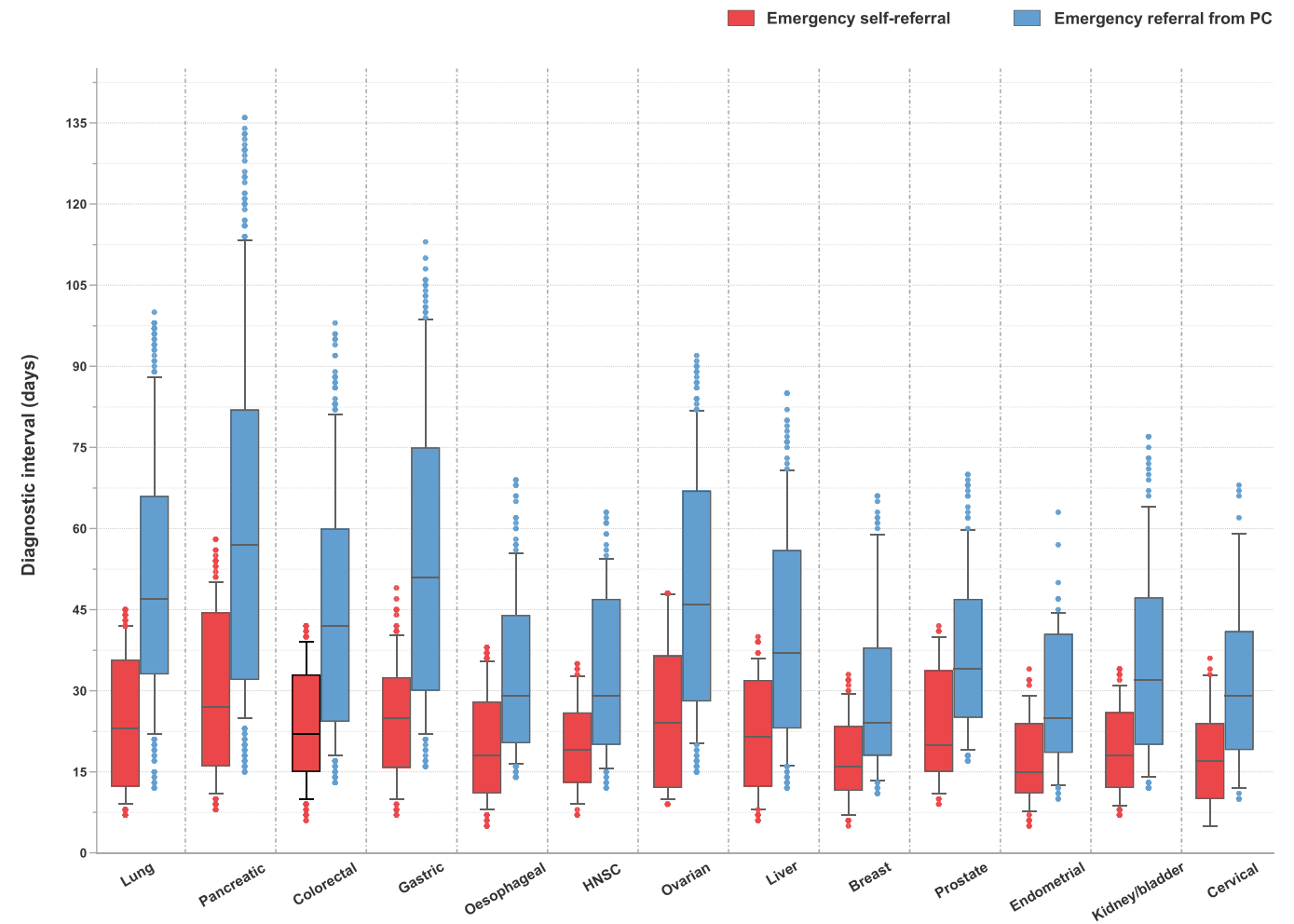


Fig. 2. Box and whisker plot showing the median diagnostic interval (in days) for each cancer type in patients diagnosed following emergency self-referral (n = 1349) and emergency referral from primary care (n = 2275). Boxes extend from the 25th to 75th percentile of each data set and horizontal lines are the median. Whiskers extend to the 10th and 90th percentiles and single data points outside whiskers are outliers. Abbreviations: PC, primary care; HNSC, head/neck squamous cell cancers.

Table 4

Total time to diagnosis (in days), overall and by cancer type, in patients diagnosed with cancer following emergency self-referral (n = 1349) and patients referred to the emergency department after consulting one or more times in primary care (n = 2275).

Cancer Type	ESR			ERPC			Difference (95 % CI)*
	50th	IQR	90 th	50th	IQR	90 th	
Overall	46	33–60	71	66	48–89	112	-20 (-22 to -19)
Lung	44.5	30–55	68	71	54.5–93.5	114	-28 (-33 to -24)
Pancreatic	51	39–64.5	80	81	55–104	136.5	-29 (-35 to -24)
Colorectal	53	43–70	86	76	53–101	125	-20 (-25 to -15)
Gastric	50.5	39–62	72.5	78	52.5–102	127.5	-27 (-34 to -21)
Oesophageal	48	34–61	73	57	44–74	96.5	-11 (-16 to -6)
HNSC	49.5	33.5–63	70.5	62	50–78	96	-14 (-21 to -7)
Ovarian	52	39.5–66.5	81	73	54–96	111	-21 (-27 to -14)
Liver	46	34.5–58	68	63	49–84	103.5	-19 (-25 to -13)
Breast	35	25.5–48	54.5	46	33–58	77.5	-11 (-16 to -6)
Prostate	44	34–58	65	56	46–71	80	-12 (-16 to -7)
Endometrial	32.5	24.5–44.5	54	45	35–55.5	71.5	-11 (-16 to -6)
Kidney/bladder	38	29–50	59	52.5	40–66.5	84	-15 (-19 to -10)
Cervical	40	27–46	58.5	50	37–73.5	85.5	-12 (-22 to -3)

* Median of the difference between intervals (Hodges-Lehmann estimate). Abbreviations: ESR, emergency self-referral; ERPC, emergency referral from primary care; IQR, interquartile range; CI, confidence interval; HNSC, head/neck squamous cell cancers.

from primary care before being referred as an emergency experienced significantly longer diagnostic delays than those who self-referred. However, since the diagnostic interval for these patients starts upon

their arrival at the emergency department rather than at primary care, we judge it as an unreliable indicator for assessing the emergency self-referral pathway.

Delving into the circumstances leading up to emergency self-referral may expose underlying factors that heighten the risk, yielding insights to guide research, clinical practice, and system-level interventions.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement

The Ethics Research Committee of Hospital Clínic of Barcelona approved the study. Based on the study design and deidentification of patient data, patient informed consent was waived.

CRediT authorship contribution statement

Alfonso Lopez-Soto: Writing – review & editing, Supervision, Methodology, Conceptualization. **Pedro Moreno:** Writing – review & editing, Methodology. **José Naval-Álvarez:** Writing – review & editing, Data curation. **Tiago Mota Gomes:** Writing – review & editing, Formal analysis. **Elisabet Montori:** Writing – review & editing, Investigation, Data curation. **Xavier Bosch:** Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.canep.2024.102609](https://doi.org/10.1016/j.canep.2024.102609).

References

- [1] S. McPhail, L. Elliss-Brookes, J. Shelton, et al., Emergency presentation of cancer and short-term mortality, *Br. J. Cancer* 109 (2013) 2027–2034, <https://doi.org/10.1038/bjc.2013.569>.
- [2] S. McPhail, R. Swann, S.A. Johnson, et al., Risk factors and prognostic implications of diagnosis of cancer within 30 days after an emergency hospital admission (emergency presentation): an International Cancer Benchmarking Partnership (ICBP) population-based study, *Lancet Oncol.* 23 (2022) 587–600, [https://doi.org/10.1016/S1470-2045\(22\)00127-9](https://doi.org/10.1016/S1470-2045(22)00127-9).
- [3] B. Danckert, A.Z. Falborg, N.L. Christensen, et al., Routes to diagnosis and the association with the prognosis in patients with cancer - A nationwide register-based cohort study in Denmark, *Cancer Epidemiol.* 74 (2021) 101983, <https://doi.org/10.1016/j.canep.2021.101983>.
- [4] Y. Zhou, G.A. Abel, W. Hamilton, et al., Diagnosis of cancer as an emergency: a critical review of current evidence, *Nat. Rev. Clin. Oncol.* 14 (2017) 45–56, <https://doi.org/10.1038/nrclinonc.2016.155>.
- [5] G. Lyratzopoulos, C.L. Saunders, G.A. Abel, Are emergency diagnoses of cancer avoidable? A proposed taxonomy to motivate study design and support service improvement, *Future Oncol.* 10 (2014) 1329–1333, <https://doi.org/10.2217/fon.14.80>.
- [6] A. Herbert, G.A. Abel, S. Winters, S. McPhail, L. Elliss-Brookes, G. Lyratzopoulos, Cancer diagnoses after emergency GP referral or A&E attendance in England: determinants and time trends in Routes to Diagnosis data, 2006–2015, *Br. J. Gen. Pract.* 69 (2019) e724–e730, <https://doi.org/10.3399/bjgp19X705473>.
- [7] G.A. Abel, S.C. Mendonca, S. McPhail, Y. Zhou, L. Elliss-Brookes, G. Lyratzopoulos, Emergency diagnosis of cancer and previous general practice consultations: insights from linked patient survey data, *Br. J. Gen. Pract.* 67 (2017) e377–e387, <https://doi.org/10.3399/bjgp17X690869>.
- [8] P. Murchie, S.M. Smith, M.S. Yule, et al., Does emergency presentation of cancer represent poor performance in primary care? Insights from a novel analysis of linked primary and secondary care data, *Br. J. Cancer* 116 (2017) 1148–1158, <https://doi.org/10.1038/bjc.2017.71>.
- [9] R.D. Neal, P. Tharmanathan, B. France, et al., Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review, *Br. J. Cancer* 112 (Suppl 1) (2015) S92–S107, <https://doi.org/10.1038/bjc.2015.48>.
- [10] M.L. Tørring, A.Z. Falborg, H. Jensen, et al., Advanced-stage cancer and time to diagnosis: an International Cancer Benchmarking Partnership (ICBP) cross-sectional study, *Eur. J. Cancer Care (Engl.)* 28 (2019) e13100, <https://doi.org/10.1111/ecc.13100>.
- [11] T.M. Pham, M. Gomez-Cano, T. Salika, D. Jardel, G.A. Abel, G. Lyratzopoulos, Diagnostic route is associated with care satisfaction independently of tumour stage: evidence from linked English Cancer Patient Experience Survey and cancer registration data, *Cancer Epidemiol.* 61 (2019) 70–78, <https://doi.org/10.1016/j.canep.2019.04.011>.
- [12] S.W. Hargarten, M.J. Richards, A.J. Anderson, Cancer presentation in the emergency department: a failure of primary care, *Am. J. Emerg. Med.* 10 (1992) 290–293, [https://doi.org/10.1016/0735-6757\(92\)90004-h](https://doi.org/10.1016/0735-6757(92)90004-h). Erratum in: *Am. J. Emerg. Med.* 11 (1993) 98.
- [13] T. Round, C. Gildea, M. Ashworth, H. Møller, Association between use of urgent suspected cancer referral and mortality and stage at diagnosis: a 5-year national cohort study, *Br. J. Gen. Pract.* 70 (2020) e389–e398, <https://doi.org/10.3399/bjgp20X709433>.
- [14] J. Lai, V. Mak, C.J. Bright, G. Lyratzopoulos, L. Elliss-Brookes, C. Gildea, Reviewing the impact of 11 national Be Clear on Cancer public awareness campaigns, England, 2012 to 2016: a synthesis of published evaluation results, *Int. J. Cancer* 148 (2021) 1172–1182, <https://doi.org/10.1002/ijc.33277>.
- [15] M.M. Koo, K. Unger-Saldana, A.D. Mwaka, et al., Conceptual framework to guide early diagnosis programs for symptomatic cancer as part of global cancer control, *Jco. Glob. Oncol.* (7) (2021) 35–45, <https://doi.org/10.1200/GO.20.00310>.
- [16] D. Weller, P. Vedsted, G. Rubin, et al., The Aarhus statement: improving design and reporting of studies on early cancer diagnosis, *Br. J. Cancer* 106 (2012) 1262–1267, <https://doi.org/10.1038/bjc.2012.68>.
- [17] X. Bosch, J. Aibar, S. Capell, A. Coca, A. López-Soto, Quick diagnosis units: a potentially useful alternative to conventional hospitalisation, *Med. J. Aust.* 191 (2009) 496–498, <https://doi.org/10.5694/j.1326-5377.2009.tb02912.x>.
- [18] International Agency for Research on Cancer (IARC), Global Cancer Observatory: Spain (2022), <https://gco.iarc.who.int/media/globocan/factsheets/populations/724-spain-fact-sheet.pdf> (accessed 4 June 2024).
- [19] G. Lyratzopoulos, G.A. Abel, S. McPhail, R.D. Neal, G.P. Rubin, Measures of promptness of cancer diagnosis in primary care: secondary analysis of national audit data on patients with 18 common and rarer cancers, *Br. J. Cancer* 108 (2013) 686–690, <https://doi.org/10.1038/bjc.2013.1>.
- [20] S.C. Mendonca, G.A. Abel, C.L. Saunders, J. Wardle, G. Lyratzopoulos, Pre-referral general practitioner consultations and subsequent experience of cancer care: evidence from the English Cancer Patient Experience Survey, *Eur. J. Cancer Care (Engl.)* 25 (2016) 478–490, <https://doi.org/10.1111/ecc.12353>.
- [21] G. Lyratzopoulos, R.D. Neal, J.M. Barbiere, G.P. Rubin, G.A. Abel, Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England, *Lancet Oncol.* 13 (2012) 353–365, [https://doi.org/10.1016/S1470-2045\(12\)70041-4](https://doi.org/10.1016/S1470-2045(12)70041-4).
- [22] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J. Chronic Dis.* 40 (1987) 373–383, [https://doi.org/10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8).
- [23] J.D. Brierley, M.K. Gospodarowicz, C. Wittekind, TNM Classification of Malignant Tumours, eighth ed., Wiley-Blackwell, Hoboken, 2016.
- [24] National Institute for Health and Care Excellence, Suspected Cancer: Recognition and Referral (2015), <https://www.nice.org.uk/guidance/ng12> (accessed 4 June 2024).
- [25] E.L. Lehmann, Nonparametric confidence intervals for a shift parameter, *Ann. Math. Stat.* 34 (1963) 1507–1512.
- [26] J.L. Hodges, E.L. Lehmann, Estimates of location based on rank tests, *Ann. Math. Stat.* 34 (1963) 598–611.
- [27] M.M. Koo, W. Hamilton, F.M. Walter, G.P. Rubin, G. Lyratzopoulos, Symptom signatures and diagnostic timeliness in cancer patients: a review of current evidence, *Neoplasia* 20 (2018) 165–174, <https://doi.org/10.1016/j.neo.2017.11.005>.