The impact of the first COVID-19 wave on the diagnostic trajectory of breast cancer in the Netherlands

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List of abbreviations

COVID-19	Coronavirus disease 2019
Sars-CoV-2	Severe acute respiratory syndrome coronavirus
DCIS	Ductal carcinoma in situ
IKNL	Integraal Kankercentrum Nederland
GP	General practitioner
IP	Patient interval
IPC	Primary care interval
DICKENS	Diagnostic Intervals in the Cancer Care Pathway in the Netherlands
EHR	Electronic Health Records
ICPC-2	International Classification of Primary Care-2
SOAP	Subjective, Objective, Assessment, Plan
IQR	Interquartile Ranges
SD	Standard Deviation
N	Number
P75	75^{th} percentile
P90	90^{th} percentile
RR	Relative Risk
95%-CI	95%-Confidence Interval
SPSS	Statistical Package for the Social Sciences

Abstract

Introduction Breast cancer is the most common form of cancer in women. From the start of the COVID-19 pandemic, healthcare was reorganized and diagnoses of breast cancer were decreased. The aim of this report is to assess the impact of the first COVID-19 wave on the diagnostic trajectory of symptomatic breast cancer patients in primary care in the Netherlands.

Method A retrospective cohort study was performed using Electronic Health Records to identify symptomatic patients with breast cancer. Those patients were internally validated. The primary outcomes were the patient and the primary care interval. Furthermore, the stratified and long durations were assessed, and the data was compared to DICKENS-1.

Results A total of 158 symptomatic breast cancer patients were identified. The IP was 18 days (IQR 4-37) and the IPC was 1 day (IQR 1-2). Compared to DICKENS-1 the IPC was significantly longer (p-value 0.026). Less than four consults in the year before COVID-19 was associated with a shorter IP. A factor associated with a long duration of the IP was breast cancer related comorbidities. A non-physical first consults and no alarm symptoms were associated with a longer IPC and with a higher risk of having a long duration.

Conclusion The COVID-19 pandemic had an impact on prolonging the IPC of patients with breast cancer, but not on the IP. Future research should be focused on defining reasons for this prolongation and developing support for GPs to diagnose the patients at risk for a long duration.

Introduction

On the 27th of February 2020 the first patient in the Netherlands was diagnosed with coronavirus disease 2019 (COVID-19)(1). This disease is caused by the severe acute respiratory syndrome coronavirus (Sars-CoV-2)(2). From the first infection, the disease spread rapidly through the country(1,3). The Dutch government took measurements in an attempt to slow down this spread and relieve the burden on hospitals(4), including social distancing, working from home and wearing face masks(5). The healthcare system was organized to care for the large amount of COVID-19 patients in the hospitals, and as a result, standard care was often postponed, including cancer care, with harmful consequences for patients(4,6).

Breast cancer, including the non-invasive form ductal carcinoma in situ (DCIS), is the most common form of cancer in women(7). Since 1989 the incidence of breast cancer in the Netherlands has doubled(8). According to the Integraal Kankercentrum Nederland (IKNL) the incidence in 2019 was 17,272 patients(8). In the Netherlands, screening for breast cancer is offered every 2-3 years to women aged 50 to 75 years, with an aim to diagnose early stages of breast cancer(9). Breast cancer diagnosed through screening is predominantly lower stages(10). Higher stages of breast cancer are often discovered through symptomatic presentations(9).

Monthly percentage of new breast cancer patients, including DCIS, in 2020 compared to 2017-2019

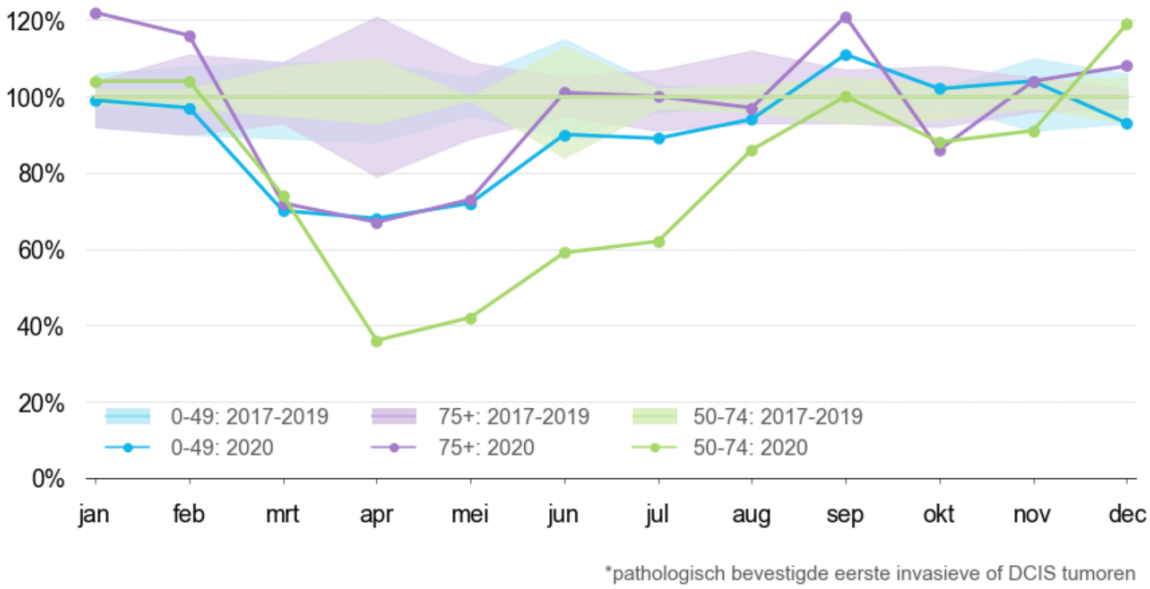

Figure 1: Percentage of new diagnosed patients with breast cancer and DCIS per month in 2020 compared to the incidence in 2017-2019(9).

As well as the reorganisation of the health care system during the COVID-19 pandemic, screening for breast cancer was stopped in March to June 2020(9). Together this resulted in a 13% decrease in new breast cancer diagnoses in 2020(8,9,11). The decrease in number of diagnosis was less extensive for higher stages of breast cancer than for lower stages(9). The 10-year survival rate of low stage tumours (stage I and II) is 85-95%, while stage IV tumours have a 10-year survival rate of 12%(12). The early detection of breast cancer is valuable because it translates to better mortality outcomes, less invasive treatments, less relapses and less complications after treatment(13).

In the Netherlands, patients with symptoms of the breast or nipples present themselves at the general practice(14,15). Thereafter, the general practitioner (GP) initiates diagnostic work-up based

on the symptoms(16). According to the Dutch College of General Practice a women presenting at the GP with a lump in the breast has a 8-9% chance of having breast cancer, which is largely dependent on age(17). Patients participating in the health care screening may also present themselves at the general practitioner if they need a referral to the hospital(17,18).

The Aarhus statement defines milestones and matching time intervals for the diagnostic route for cancer diagnosis, including the 'patient interval' and the 'primary care interval'(19). The patient interval (IP) starts at the patient first noticing a symptom and ends the first presentation of the patient at the general practitioner with this symptom(19). This is when the primary care interval (IPC) starts. This interval ends when the GP refers to the secondary care and thereby referring the responsibility(19).

The COVID-19 pandemic has an impact on breast cancer diagnostic pathways, as identified through the reduction in diagnoses in 2020. Yet the extend of this impact, and which care systems it has disrupted remain unclear. The aim of this report is to assess the impact of the COVID-19 pandemic in the diagnostic trajectory in primary care of breast cancer in the period from the 1st of March to the 30th of June 2020 in the Netherlands.

Method

Design and data sources:

A retrospective cohort study was performed as a sub-analysis of the DICKENS-2 study (Diagnostic Intervals in the Cancer Care Pathway in the Netherlands during COVID-19). Data from the Intercity Database were used. This is a database consisting of anonymized Electronic Health Records (EHR) from five academic GP networks. The EHR contain coded and non-coded information. The coded information consisted of International Classification of Primary Care (ICPC-2) codes(20). The non-coded information was free text written by GPs or assistants, letters from specialists and referrals. The 'SOAP' was used by GPs for a systematic report. This is an acronym that stands for 'Subjective' (symptoms and duration), 'Objective' (physical exams), 'Assessment' (clinical reasoning) and 'Plan' (taken actions)(21).

Case selection:

Adult patients were initially selected from the database by the recurrence of the ICPC code X76 'Malignant neoplasm breast female' from the start of the first COVID-19 period at 1st of March 2020, until the date whereafter nobody could be included for two months. This was the 31st of March 2021. Both patients presenting with symptoms and patients detected through the health care screening for breast cancer were included.

By evaluating the free text in the EHR the diagnosis breast cancer was confirmed. This is called internal validity. This was obtained through letters from secondary care, notes from the GP or telephone consults. Patients were excluded if there was no evidence for internal validation, relevant data was missing, the GP was not involved in the diagnostic work-up, the breast cancer was an incidental finding, the patient was diagnosed internationally, or the entire diagnostic trajectory took place before or after the first COVID-19 wave.

Data collection:

The data from the EHR was evaluated by a sixth-year medical student. Following a data collection guide the relevant data were collected into Castor-ED, with a focus on the duration of the diagnostic trajectory. Castor-ED is a secure online data repository(22). In case of doubt, a discussion in the research group followed.

Time intervals:
The used time intervals were defined by milestones. The patient interval (IP) started with the patient noticing the first symptoms and ends with the first presentation at the GP. The primary care interval (IPC) was defined as the period between the first presentation at the GP and the first referral to secondary care, as shown in Figure 2.

Milestones and time intervals according to the Aarhus statement

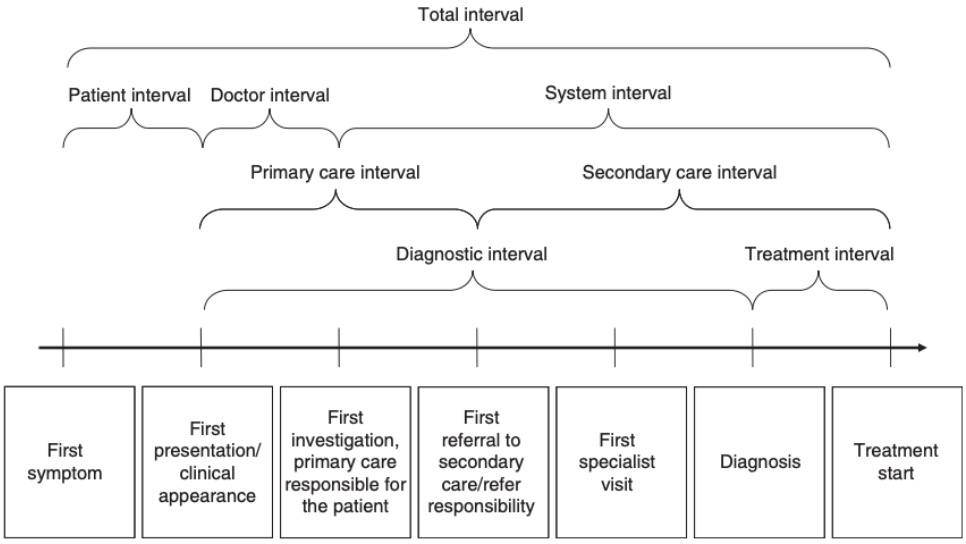

Figure 2: The milestones and time intervals according to the Aarhus statement, especially the patient and primary care interval(19).

According to the Aarhus statement, the date of the first symptoms is *'the time point when first bodily changes and/or symptoms are noticed'*(19). These changes or symptoms had to be related to breast cancer or metastasis of breast cancer. The free text of the EHR were assessed for duration of the symptoms at the first consultation. Occasionally, the exact date or duration of the symptoms was missing or vaguely described. In these cases, the duration was determined through agreements (Appendix 1).

The first presentation at the GP is *'the time point at which, given the presenting signs, symptoms, history and other risk factors, it would be at least possible for the clinician seeing the patient to have started investigation or referral for possible important pathology, including cancer'*(19). This could be a physical or telephone consult. The patients presenting through the health care screening for breast cancer, the date on which the GP was informed about the result is registered.

The date of referral is *'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, relating to the patient's suspected cancer'*(19). This could be a referral to a specialist or a referral for additional testing. When abnormal test results led to a referral to a specialist, without intervention of the GP, the date of the test order was considered the date of referral.

Patient characteristics:
Patient characteristics were extracted from the EHR, including age, sex, history of cancer and comorbidities according to O'Halloran et al(23). The comorbidities were divided in chronic, breast cancer specific and psychiatric comorbidities. Furthermore, the symptoms related to breast cancer, their duration and the date of a possible referral were registered. The symptoms were subdivided in site related alarm symptoms, generalized alarm symptoms, site related non-alarm symptoms and

non-site related non-alarm symptoms (Appendix 2). As additional outcomes the number and type (physical or non-physical) of consultations pre-COVID and during COVID were measured and reasons for (COVID-related) delay were registered.

Analysis:
Descriptive statistics were used to describe baseline characteristics for the symptomatic patients. The measures used for these characteristics were median and interquartile ranges (IQR), mean and standard deviation (SD) or number (N) and percentage (%).

The IP and IPC durations were calculated for each patient. One day was added to all intervals, because a consultation and referral on the same day was considered as one day. The results were reported in days with a median, interquartile ranges, and a P90, as we suspected our data was right skewed.

Subsequently, the characteristics were classified in disease and patient characteristics. With the Mann-Whitney U-test and Kruskall-Wallis test an association was assessed (significant association when $p<0,05$).

A long duration for both intervals was defined as a duration equal or above the 75^{th} percentile (≥P75). With a univariate analysis an association between the characteristics and a long duration was evaluated. The association was expressed in a relative risk (RR), corresponding 95%-Confidence Intervals (95%-CI) and a p-value. Logistic regression was used to estimate significance associations.

Furthermore, the IP and IPC calculated in DICKENS-1(24) were compared to the IP and IPC during the first period of COVID-19 using chi-squared testing. A significant difference was defined as a p-value smaller dan 0,05. DICKENS-1 is a study performed pre-COVID that used the same method, the same definitions for the intervals and the same database(24).

SPSS version 26.0 software was used for the statistical analysis.

Results

Case selection
A total of 837 patients were identified with an ICPC-2 code for X76 ‘Malignant neoplasm breast female’ between 01-03-2020 and 31-03-2021. Of those patients, 178 patients had no or doubtful internal validation or data were missing, resulting in 659 patients with the diagnosis breast cancer internally validated. Figure 3 shows that eventually 158 patients presenting themselves symptomatically at the GP or emergency GP were included in this study.

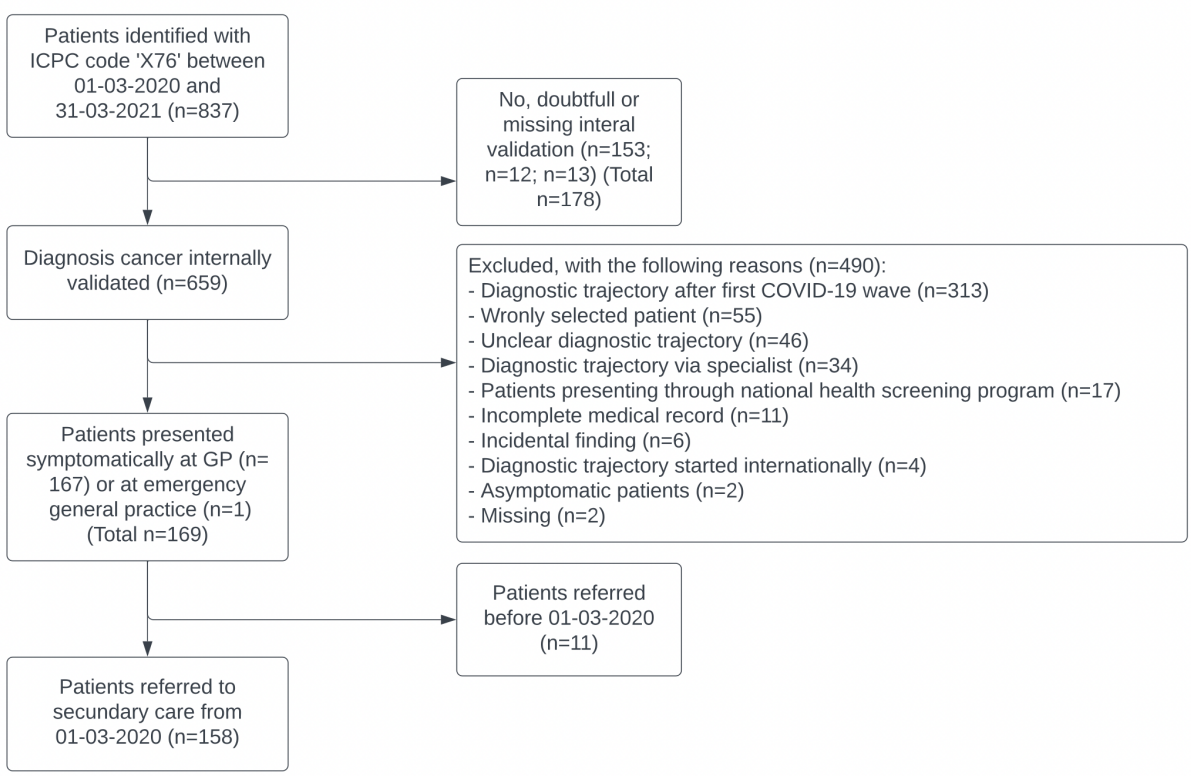

Figure 3: Flowchart of patient selection. N = number; GP = general practitioner.

All the patients were female, with a mean age of 58.9 years and a standard deviation (SD) of 17.4 years. 57.6% of the patients had no or one somatic comorbidity, 91.1% had no breast cancer related comorbidities and 67.6% of the patients had no psychiatric comorbidities. Table 1 describes more demographic and clinical characteristics of the cohort, comparing them to the DICKENS-1 population. There were significant differences between the baseline characteristics in DICKENS-1 and DICKENS-2 concerning the number of breast cancer related comorbidities and the psychiatric comorbidities.

	DICKENS-2	**DICKENS-1**	**p-value**
***Total population** N (%)*	**158 (100.0)**	**306 (100.0)**	
***Gender** N (%)*			NA
- *Female*	158 (100.0)	306 (100.0)	
***Age** mean (SD)*	58.9 (17.4)	57.5 (18.2)	
- *<50 N (%)*	58 (36.7)	130 (42.5)	0.471
- *50-75 N (%)*	64 (40.5)	110 (35.9)	
- *>75 N (%)*	36 (22.8)	66 (21.6)	
***Somatic comorbidities** N (%)*			0.055
- *<2*	91 (57.6)	146 (47.7)	
- *≥2*	67 (42.4)	157 (51.3)	
***Breast cancer related comorbidities** N (%)*			0.006
- *No*	144 (91.1)	254 (83.0)	
- *Yes*	11 (7.0)	49 (16.0)	
***Psychiatric comorbidities** N (%)*			0.001
- *No*	107 (67.7)	251 (82.0)	
- *Yes*	47 (29.7)	52 (17.0)	

Previous malignancy *N (%)*			0.832
- *No*	135 (85.4)	280 (91.5)	
- *Yes*	12 (7.6)	23 (7.5)	
Family history of breast cancer *N (%)*			0.588
- *No*	55 (34.8)	89 (29.1)	
- *Yes*	33 (20.9)	62 (20.3)	
Number of consults in year before COVID-19 *N (%)*		NA	NA
- *<4*	54 (34.2)		
- *≥4*	95 (60.1)		
Region *N (%)*			NA
- *Utrecht*	51 (32.3)	279 (91.2)	
- *Amsterdam (AMC)*	34 (21.5)	0 (0)	
- *Amsterdam (VUmc)*	35 (22.2)	27 (8.8)	
- *Groningen*	22 (13.9)	0 (0)	
- *Maastricht*	16 (10.1)	0 (0)	

Table 1: Baseline table with patient characteristics of DICKENS-1 and DICKENS-2 and a corresponding p-value. N = number; SD = standard deviation; NA = not applicable.

Duration of diagnostic intervals

The median duration of the patient interval and the primary care interval, with corresponding IQR are shown in Table 2. The IP and IPC were only analyzed for the patients with an IP or an IPC occurring within the first wave of COVID-19. For DICKENS-2 the IP was computable for 123 patients. The median duration was 18 days, with IQR of 4 – 37 days and a P90 of 93 days. For DICKENS-1 the median IP duration was not significantly lower, that is 15 days, with IQR of 4 – 32 days and a P90 of 123 days (p-value = 0.451). The IPC for DICKENS-2 was computable for 145 patients. The median IPC was 1 day, with IQR of 1 – 2 days and a P90 of 18 days. For DICKENS-1 the IPC was computable for 306 patients, with an IPC of 1 day, an IQR of 1 – 1 day and a P90 of 17 days which was significant (p-value = 0.026).

	IP in days			**IPC in days**		
	DICKENS-2	DICKENS-1	p-value	DICKENS-2	DICKENS-1	p-value
Computable for n	123	169	0.451	145	306	0.026
Median (IQR; P90)	18 (4 – 37; 93)	15 (4 – 32; 123)		1 (1 – 2; 18)	1 (1 – 1; 17)	

Table 2: Median IP and IPC, with IQR and P90 for DICKENS-1 and DICKENS-2. IP = patient interval; IPC = primary care interval; n = number; IQR = interquartile range; P90 = 90th percentile.

Patient interval stratified for characteristics

Median

Table 3 shows the median duration of the IP, with corresponding IQR and P90. The median IP is significantly shorter for the patients who had ≥4 consults in the year before the first COVID-19 wave, respectively 8 days or 22 days. Patients who had a non-physical consult as a first consult had the shortest median IP of 5 days, compared to a first physical consult with a median IP of 20 days,

although this was not statistically significant. Patients who had a history of breast cancer related comorbidities had a longer median IP of 92 days, compared to 15 days in patients with no breast cancer related comorbidities, which is approaching statistical significance.

	N =	Median IP duration in days (IQR; P90)	p-value	Univariate analysis for IP >P75, RR (95%-CI)	p-value
Total population	123	18 (4 – 37; 93)			
Age			0.924		
- *<50*	48	15 (4 – 43; 93)		Ref.	
- *50-75*	48	18 (4 – 55; 93)		0.92 (0.47 – 1.81)	0.816
- *>75*	25	15 (4 – 30; 155)		0.74 (0.30 – 1.84)	0.514
Nature of first consult			0.380		
- *Non-physical*	17	5 (3 – 76; 111)		Ref.	
- *Physical*	104	20 (4 – 36; 93)		0.82 (0.36 – 1.84)	0.626
Alarm symptoms			0.253		
- *No*	15	22 (5 – 91; 495)		Ref.	
- *Yes*	106	12 (4 – 33; 93)		0.71 (0.32 – 1.56)	0.393
Number of consults in year before COVID-19			0.041		
- *<4*	44	22 (8 – 80; 138)		Ref.	
- *≥4*	71	8 (4 – 29; 92)		0.67 (0.35 – 1.28)	0.226
Somatic comorbidities			0.215		
- *<2*	74	22 (4 – 48; 93)		Ref.	
- *≥2*	47	8 (4 – 37; 101)		0.91 (0.48 – 1.74)	0.779
Breast cancer related comorbidities			0.058		
- *No*	115	15 (4 – 31; 92)		Ref.	
- *Yes*	6	92 (17 – 162)		3.07 (1.58 – 5.96)	0.001
Psychiatric comorbidities			0.612		
- *No*	85	15 (4 – 52; 92)		Ref.	
- *Yes*	35	15 (4 – 31; 256)		0.53 (0.22 – 1.28)	0.156
Previous malignancy			0.282		
- *No*	105	21 (4 – 40; 93)		Ref.	
- *Yes*	9	8 (3 – 22)		0.45 (0.07 – 2.93)	0.403
Family history for breast cancer			0.347		
- *No*	48	12 (4 – 57; 93)		Ref.	
- *Yes*	27	8 (4 – 22; 61)		0.41 (0.13 – 1.31)	0.133

Table 3: Median IP duration in days, with corresponding IQR and P90, and the relative risk per characteristic of belonging in the >P75 group. IP = patient interval; IQR = interquartile range; P90 = 90th percentile; P75 = 75th percentile; RR = relative risk; 95%-CI = 95% confidence interval.

Long duration

Using a univariate log-binomial regression analysis, characteristics potentially associated with a long duration (>P75) were detected as shown in Table 3. Having one or more breast cancer related comorbidity was significantly associated with a 3.07 times higher risk of having a long IP duration.

Primary care interval stratified for characteristics

Median

In Table 4 the median IPC duration in days, with corresponding IQR and P90, is shown. A physical first consult and presence of alarm symptoms were significantly associated with a shorter median IPC. Patients with a physical first consult had a median IPC of 1 day, instead of 4 days for patients with a non-physical consult. The presence of alarm symptoms did not change the median IPC for patients (both a median of 1 day), but the P75 and P90 were 1 and 15 days in patients with alarm symptoms, against 49 and 284 days in patients without alarm symptoms.

	N =	Median IPC duration in days (IQR; P90)	p-value	Univariate analysis for IPC >P75, RR (95%-CI)	p-value
Total population	145	1 (1 – 2; 18)			
Age			0.388		
- *<50*	54	1 (1 – 2; 65)		Ref.	
- *50-75*	59	1 (1 – 1; 15)		0.73 (0.38 – 1.42)	0.357
- *>75*	32	1 (1 – 5; 15)		1.24 (0.65 – 2.56)	0.516
Nature of first consult			0.000		
- *Non-physical*	20	4 (2 – 15; 142)		Ref.	
- *Physical*	125	1 (1 – 1; 15)		0.20 (0.13 – 0.30)	0.000
Alarm symptoms			0.020		
- *No*	20	1 (1 – 49; 284)		Ref.	
- *Yes*	124	1 (1 – 1; 15)		0.50 (0.28 – 0.90)	0.021
Number of consults in year before COVID-19			0.315		
- *<4*	45	1 (1 – 1; 21)		Ref.	
- *≥4*	93	1 (1 – 2; 18)		1.40 (0.72 – 2.73)	0.327
Somatic comorbidities			0.949		
- *<2*	82	1 (1 – 2; 15)		Ref.	
- *≥2*	63	1 (1 – 2; 42)		0.95 (0.54 – 1.65)	0.846
Comorbidities relevant for breast cancer			0.387		
- *No*	133	1 (1 – 2; 15)		Ref.	
- *Yes*	9	1 (1 – 39)		1.34 (0.51 – 3.54)	0.551
Psychiatric comorbidities			0.472		
- *No*	98	1 (1 – 2; 17)		Ref.	
- *Yes*	43	1 (1 – 1; 18)		0.76 (0.39 – 1.48)	0.417
Previous malignancy			0.518		
- *No*	122	1 (1 – 2; 19)		Ref.	
- *Yes*	12	1 (1 – 8; 294)		1.31 (0.56 – 3.09)	0.534
Family history for breast cancer			0.349		
- *No*	49	1 (1 – 1; 15)		Ref.	
- *Yes*	33	1 (1 – 2; 18)		1.19 (0.52 – 2.69)	0.680

Table 4: Median IPC duration in days, with corresponding IQR and P90, and the relative risk per characteristic of belonging in the >P75 group. IPC = primary care interval; IQR = interquartile range; P90 = 90th percentile; P75 = 75th percentile; RR = relative risk; 95%-CI = 95% confidence interval

Long duration
In Table 4 characteristics potentially associated with a long IPC duration (>P75) were identified using univariate log-binomial regression analysis are shown. Having a physical first consult and the presence of alarm symptoms were significantly associated with having diminished risk (RR = 0.20 and 0.50) of belonging in the long duration group.

Discussion
Summary of main findings:
Patients with symptomatic breast cancer during the first wave COVID-19 pandemic do not have a significantly longer patient interval. On the other hand, the duration of the primary care interval, when occurring during the COVID-19 pandemic, is significantly longer than the primary care intervals before the COVID-19 pandemic. Patients with breast cancer related comorbidities have a significantly higher change to have a duration above the P75. In the same way patients with a non-physical first consult and patients with no alarm symptoms have a significantly higher change to have a long median IPC and a duration >P75.

Comparison with literature:
The patient interval is not significantly prolonged during COVID-19, which contradicts the hypothesis of this study. There was a suspicion that patients would avoid meeting people, including the GP, because of a fear to be infected with COVID. According to Splinter et al. approximately 20% of the patients in the Netherlands avoided healthcare during the COVID-19 pandemic, of which being older and female was associated with more avoidance(25). The explanation for the similarity of the IP pre- and during COVID-19 is unclear. However, it could have several reasons. Firstly, breast cancer is a cancer form that is often discussed in the news or on social media, which raises awareness between women. This awareness results in women detecting early changes in their breasts and realizing the importance to go to the GP with these symptoms.(26,27) Another explanation is that the registration and interpretation of the start of the patient interval is subject to bias at multiple points. The GP had to ask the patient when the symptoms started, the patient had to properly remember the date of the first symptom, the GP had to record that date or duration and then the researchers had to interpret this duration. This could lead to an underestimation of the time from the fist symptom to presentation.

Having one or more breast cancer related comorbidities is associated with a long duration of the patient interval. A reason for this prolongation is that the patient thinks the newly onset symptom is an expression of the already existing breast cancer related comorbidity. Another explanation for the delay, is that patients with breast cancer related comorbidities will in a later stage become aware of their cancer symptom, because the comorbidity will mask this symptom. This is slightly different from Flemming et al. stating that patients having breast cancer related comorbidities are less likely to be diagnosed with an advanced stage of breast cancer(28). A delay in presentation could be related to a higher stage of breast cancer according to Burgess et al.(29).

Having had four or more consults in the year before COVID-19 is associated with a significantly shorter IP. Patients who have a higher consult density, are more likely to present themselves with early stages of a symptom. Another reason for this association is that patients who visit the GP more often, are more likely to be concerned about their health and want the GP to assess every symptom.

The prolongation of the primary care interval during COVID-19 is in line with the hypothesis of this study. Even though there was a significant prolongation, from a clinical perspective the delay was very limited. Possible explanations for the prolongation include patients having COVID related symptoms, a positive test result for COVID or quarantine obligations and therefore had to move their appointment(30). Another reason for the longer IPC is that there was a significant difference

between the patient population of DICKENS-1 and DICKENS-2 regarding the breast cancer related comorbidities and the psychiatric comorbidities. As mentioned before, breast cancer related comorbidities could delay the diagnostic trajectory, because the patient, as well as the GP, could link the symptoms to the already known comorbidity. In the patient population of DICKENS-1 there are more patient without a psychiatric comorbidity contrary to the patient population of DICKENS-2. A psychiatric comorbidity could play a role in the duration of the referral, because the patients' behavior during the consult could influence the reasoning of the GP and postpone a referral(15). According to Van Hout, Van Erp and Iglay, psychiatric comorbidities could result in a doctors diagnostic delay with regard to cancer(31–33).

Factors that are associated with a prolonged IPC and belonging to the long duration group of the primary care interval are a non-physical first consult and no alarm symptoms. An explanation for these prolonging factors is that patients with no alarm symptoms are not directly referred to secondary care, but there is another diagnosis matching the symptoms (34,35). As regards to the non-physical first consult, the primary care interval is longer, because a patient is referred after the GP has done a physical examination as part of the diagnostic workup in primary care (17).

Strengths and limitations:

A strength of this study was that the Electronic Health Records free text written by GP's and assistants was available. Due to this, it was possible to validate the ICPC-2 code X76 for breast cancer. It is known that not all ICPC codes are assigned correctly. In this study, this did not cause a problem. Another advantage by using the free text in the EHR is that potential considerations of the GP are also available in the diagnostic trajectory. This can be used for further qualitative research in defining delaying factors in the diagnostic trajectory in primary care during the COVID-19 pandemic.

A second strength of this study is that it is possible to compare the results with the DICKENS-1 study, which is a study using the same method, the same definitions for the intervals and the same databases. A remark connected with the comparison between DICKENS-1 and DICKENS-2 is the significant baseline differences concerning the breast cancer related comorbidities and the psychiatric comorbidities. These differences were most likely caused by improved quality of data in the DICKENS-2 study, allowing the researchers to better identify comorbidities in the patient population. However, by using the DICKENS-1 data it was possible to define the impact of COVID-19 on the diagnostic trajectory in primary care.

A third strength is the nationwide sample of the Netherlands that is used. Data is collected from multiple regions in the Netherlands, resulting in a broad representation of the people and the primary health care in the Netherlands during the COVID-19 pandemic.

This study also had limitations. These limitations are divided in two main topics, these are the retrospective design and the patient population. Firstly, the retrospective design involves difficulties. The EHR consists only of limited information, written down for medical purposes. The GP only writes down what he or she thinks is important to be noted, but a lot more can be discussed during the appointment. This could cause either an under- or overestimation of the IP and IPC. Moreover, the GP did not always write down the duration of the symptoms, this could lead to selective missing patients for the IP. Another difficulty with the registration was that sometimes the start of the symptoms was not always clearly defined. When this occurred, a discussion followed in the research group, but this could lead to an under- or overestimation of the IP or IPC. Furthermore, when the patients' diagnostic trajectory was not clear, the patient was excluded. Due to the poor registration, less patients could be included in this study, resulting in lower statistical power. Another limitation of the retrospective design is that the character of the first consult was not always recorded correctly. The character of the consult relates to the financial pathways for the general practice. During COVID-19 telephone consultations were more extensive, resulting in GPs registering a physical consult

instead of a telephone consult. Due to this, in our data there could be an underestimation of the number of non-physical consults.

The other main topic of the limitations is the patient population. Firstly, due to missing data only a little number of patients was included in this study, resulting in small groups when divided per characteristic. Only patients presenting themselves symptomatically at the GP or the emergency GP are included, so patients presenting themselves at the emergency room in the hospital. Patients at the emergency room are often sicker than in the general practice and their symptoms may exist longer. By excluding these patients, the IP and the IPC could be longer than the results of this study suggest. Patients with no referral to secondary care, for example because they refused diagnostic imaging, are excluded from this study. Their primary care interval cannot be calculated, but may be very long. This could result in a distortion of the IPC calculated in this study. Another problem regarding the patient population is the random sample taken in Amsterdam (VUmc). The dataset was chronologically ordered. There are more patients screened in the first half of the dataset, possibly resulting in more inclusions than in the second half of the dataset, from July 2020. This could lead to an underestimation of the IP and IPC, because less patients with a long duration are screened.

Implications for further research and practice:
Reducing the primary care intervals should be focussed on the long duration group. The characteristics resulting in a high risk for the long IPC duration (a non-physical first consult and no alarm symptoms during the consultation), should be detailed to GPs. For each of the patient groups, guidance could be developed to assist GPs in diagnosing these patients to minimise diagnostic delays, for example with biomarkers or artificial intelligence. Further research could include qualitative research to determine other impacts of delay during the COVID-19 pandemic, for example through interviewing patients. This could help GPs to anticipate on these factors during possible following pandemics.

Conclusion

The COVID-19 pandemic has had a prolonging impact on the primary care interval in patients with breast cancer. However, the patient interval was not significantly longer. Factors prolonging the primary care interval were having no alarm symptoms at presentation and having a non-physical first consult. Breast cancer related comorbidities was a factor influencing the duration of the patient interval. Future research should focus on defining reasons for COVID-related delay in the diagnostic trajectory in primary care, especially so that GPs are prepared for coming pandemics.

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Appendices:

Appendix 1: Agreements on duration of first symptom

	Free text in EHR	Interpretation	Rule for date registration
Acute	Since last night	0 days	Consultation date
Days	Since a couple/few days	3 days	3 days before first consultation
	Since last weekend	Saturday	Saturday before first consultation
Weeks	Since last week	7 days	7 days before first consultation
	Since the end of last week	Friday	Friday before first consultation
	For more than a week	9 days	9 days before first consultation
	For 1,5 weeks	11 days	11 days before first consultation
	Since a few/couple/several weeks	3 weeks	21 days before first consultation
Months	For one month	1 calendar month	One month earlier same date
	For more than a month	1 month and 7 days	One month earlier and 7 extra days
	For more than two months	2,5 calendar months	2,5 months earlier
	Since January	Half of the month	15th of the month (14th in February)
	Since end of January	Last day of month	30/31th
	Since a few/couple/several months	3 months	3 months earlier, same date
Years	For more than a year	1 year and 3 months	One year and 3 months earlier
	Since the beginning of the year	January 1st	First day of the year
	Since 2018	Halfway through the year	1st of July 2018
	Since years	3 years	3 years earlier, same date
	Since a few/couple/several years	3 years	3 years earlier, same date
Other	Since winter (or another season)	Start of the season	21st of December
Vague	Since a while/since a long/some time	Too vague, consider as missing, no interpretation	No registered date

Appendix 2: Categories of symptoms for breast cancer

Category of symptoms	**Symptoms**
Site related alarm symptoms	Lump in breast/armpit
Generalized alarm symptoms	Anemia Unintentional weight loss Ascites Icterus
Site related, non-alarm symptoms	All other breast-related symptoms
Non-site related, non-alarm symptoms	Back and/or joint complaints All other localized complaints Tiredness Malaise Etc