REGION KRONOBERG

Diagnostic significance of thrombocytosis in patients with suspected colorectal cancer in primary care

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Contents

Background

Colorectal cancer (CRC) is after prostate and breast cancer the third most common form of cancer in Sweden with about 6 000 new diagnoses annually [1]. It is the third leading cause of cancer-related deaths in Sweden [2] and the second worldwide [3].

Primary care plays a central role in detecting early signs and symptoms that rise suspicion of cancer. However, it is a general problem that most of the research that forms the basis for diagnostics is not based on a primary care perspective, which makes the results difficult to generalize and build diagnostic processes according to.

Aiming to create a more standardized cancer care with an increased quality and shortened waiting times, Sweden has introduced 31 cancer patient pathways (CPP) in 2015 that cover over 95% of all cancer diagnoses, including colorectal cancer. A CPP describes which symptoms and criteria constitute suspicion or well-founded suspicion of cancer, which investigations and first treatments are to be made and which maximum lead times apply to the various measures [4].

How a CPP is designed has significant implications for the practical work in healthcare. It is essential that the inclusion criteria are well investigated to reduce diagnostic delay for patients who fall outside the criteria but still have a cancerous disease. Therefore, it is important that the presence of the criteria gives a reasonably high probability of disease and that absence gives a high probability of not having the disease. From a primary care perspective, it is therefore important to identify common risk markers that could provide additional information in the diagnostic process.

A risk marker of cancer that has recently shown to have a diagnostic potential is thrombocytosis (raised platelet count). Previous studies have reported on the usefulness of platelet count as a prognostic tool in secondary care and mechanisms that could underlie this association have been explored, but it is only in recent years that the significance of an increased platelet count in primary care began to be studied. A systematic review of case control studies showed results that indicate that patients with an increased platelet count in primary care have an increased risk of cancer, and that some but not all cancers have an increased number of platelets as an early marker [5]. A subsequent large-scale prospective cohort study from primary care reported that males with

thrombocytosis had an 11.6% incidence of cancer in the following year and females an incidence of 6.2%. The most common cancers in those with an increased platelet count were lung and colorectal cancers [6]. The diagnostic significance of an increased platelet count in patients selected for a CPP has not been investigated in Sweden.

The primary aim of this study is to analyze the association between an increased platelet count and colorectal cancer in primary care patients who are referred according to colorectal CPP.

Material and methods

Setting

The study was conducted with healthcare data from Kronoberg County which has a population of 202,163 inhabitants [7]. Healthcare in the county is divided into 31 primary care centers and 2 emergency hospitals.

Kronoberg County reported 1,301 new cancer cases in 2018, of which 168 cases of colorectal cancer [1].

CPP for colorectal cancer was introduced in Kronoberg County in 2016 and it has since been revised on 3 occasions, no later than 2020-01-24. The current version with a focus on referrals from primary care considers that one of the following criteria, used individually or combined, should raise suspicion of colorectal cancer: visible blood in stool, anemia and change in otherwise stable bowel habits for >4 weeks without other explanation in patients over 50 years. When suspicion has been raised, the following must be performed within 10 calendar days: anamnesis including IBD and heredity, rectal palpation, rectoscopy and in case of anemia – anemia investigation. Well-founded suspicion of colorectal cancer occurs according to one or more of the following criteria: visible blood in stool where rectal palpation and rectoscopy do not show another obvious source of bleeding (or where bleeding persists after 4 weeks despite adequate treatment of another bleeding source), iron deficiency anemia without other obvious cause, rectoscopy or rectal palpation which leads to suspicion of colorectal cancer, findings on imaging or tissue diagnosis or colonoscopy which leads to suspicion of colorectal cancer.

If there is a well-founded suspicion, the patient must be referred immediately for further investigation according to the colorectal CPP [8].

Datacollection

For this registered based study, we selected all the patients who were referred from primary care within the colorectal CPP during the period 2018-07-01 – 2019-07-01. The cohort was a sample of

424 patients (figure 1). After excluding the patients who already have had a cancer diagnosis during the previous 5 years (n=35), other forms of cancer diagnosed parallel to the start of colorectal CPP (n=14), and referrals that were duplicated (n=5), incorrectly registered (n=4) or not investigated within CPP (n=25) 341 patients were included in the study.

The following information was registered for each individual patient: gender, age, platelet count closest to the time of the CPP referral, colorectal cancer diagnosis within 6 months after the CPP start, whether they were assessed or not within CPP in secondary care and which of the 4 criteria for well-founded suspicion of cancer they met; which from a primary care context were: rectal bleeding, iron deficiency anemia, rectal exam findings (palpation and/or rectoscopy) and diagnostic imaging findings.

Data analysis

Based on medical records data continuous variables were summarized using mean and standard deviation (SD). Patients were grouped in 3 age categories due to the distribution of the data.

Categorical data was summarized using frequencies and percentages. Comparisons between continuous variables were made using the student t-test and between categorical data using chi-squared test. The association between thrombocytosis (defined as TPK >400 x 10^9/L) and colorectal cancer was assessed with a logistic regression model and presented as odds ratio (OR) and 95% confidence interval. Crude ORs were calculated in a univariate logistic regression model for each parameter. This was followed by a bivariate logistic regression with age as second predictor. We then calculated a second multivariate regression analysis performing step-wise backward selection with all the significant parameters from the univariate regression model.

All analyses were performed with SPSS version 27.0 software (SPSS Inc., Chicago, IL, USA).

Ethical approval

Ethical committee approval was given by the Ethics Review Authority in Sweden, Etikprövningsmyndigheten: reference number 2020-06796.

Results

A total of 341 patients referred within CPP were included in the study after exclusions. Of these 45 patients (13.2%) were diagnosed with colorectal cancer.

The demographic parameters of the patients are stated in table 1. The mean age of the CRC group was significantly higher than the mean age of the non-CRC group (72.6 vs 66.1, p=0.003).
The cohort consisted of 56.3% female and 43.7% male patients. Of the patients who were diagnosed with CRC 51% were female and 49% were male (p=0.45).

Twelve patients did not have a platelet count registered. The mean platelet value was significantly higher in the CRC group (324.76 x 10^9/L vs 270.88 x 10^9/L, p=0.001 t-test). Patients in the CRC group had significantly more often thrombocytosis than patients in the non-CRC group (17.78% vs 5.99%, p=0.006).

As shown in table 1, of the 4 criteria which is included in the CPP, iron deficiency anemia (35.56% vs 21.28% p=0.003), rectal exam findings (43.33% vs 17.44% p=0.001) and diagnostic imaging findings (100% vs 28.57%) were significantly more often present in the CRC group. The number of patients with rectal bleeding did not significantly differ between the groups (56.67% vs 48.40% p=0.40). We calculated the PPVs and NPVs (table 3) which for thrombocytosis were 32% vs 87.8%.

Univariate analysis was performed to calculate crude ORs for every parameter stated above. The possible confounding of age and thrombocytosis was considered in the first multivariate model (table 3 – model 1) which shows that both factors are significantly associated with colorectal cancer. We then performed a second multivariate analysis with all the significant factors from the univariate analysis, where – after backward elimination – thrombocytosis, anemia and rectal exam findings were significantly associated with colorectal cancer (table 3 – model 2).

Discussion

To our knowledge this is the first study to investigate the role of thrombocytosis in a selected primary care population of patients in Sweden's colorectal CPP. Our study shows that thrombocytosis is strongly associated with the occurrence of colorectal cancer in patients that present other common risk factors for colorectal cancer.

One limitation of this study is that it is built on a pre-selected study population, with a high suspicion of cancer and therefore, general assumptions on the significance of thrombocytosis in cancer diagnostics cannot be made. This is for example reflected in the generally high PPV values in all the categories in this study which by far exceed the 3% threshold set by the UK NICE guidelines for the urgent investigation of cancer [9]. That thrombocytosis has a place in identifying patients at risk for colorectal cancer in an unselected population has been shown by others [6]. A recently published retrospective study from the UK with a larger, but similarly selected population as in our study came to matching results, showing an OR of 2.62 for colorectal cancer in the group of patients with thrombocytosis compared to this study's OR of 3.93 [10]. Thus, it seems that even within patient groups with a high risk for colorectal cancer, thrombocytosis can be used for further risk stratification.

Yet, in accordance with this study's results, the percentage of patients in the UK study [10] with thrombocytosis in the CRC group was only 19.2% (and 17.8% in this study), clearly showing the limitations of the parameter as a predictive factor. Another Swedish study group, primarily investigating the usefulness of faecal immunochemical tests (FIT) in symptomatic primary care patients, found – corresponding to our results – that thrombocytosis has a reasonable PPV (4.4 compared to 6.4 for positive FIT), but a low sensitivity (16.9% compared to 90.7% for positive FIT) and high, but still unsatisfactory NPV of 98.0 for colorectal cancer [11]. Thus, also in this more unselected study population, thrombocytosis cannot be used to rule out the risk for colorectal cancer. The negative predictive value of 87.8% in this study is even lower and consequently far too small to exclude those without thrombocytosis from the fast-track CPP.

Another limitation of this study is its relatively small size with the consequence that we could not adjust for potential confounding factors – as for example signs or symptoms not included in the CCP – which might have had an impact on thrombocytosis.

Criteria included in a CPP algorithm must have a high diagnostic accuracy when selecting patients to be prioritized in the diagnostic process. Only around 50% of patients who were referred according to Sweden's colorectal CPP in the last five years met the time goal to complete the fast-track investigation [12]. Shortage in colonoscopy units and specialists is thought to be one reason for this. On the other hand, between 1/4 – 1/3 of the patients who start their investigation within the colorectal CPP are diagnosed with colorectal cancer [13], showing the need to identify those with highest risk in order to optimize the colorectal CPP process. Our results show a PPV of thrombocytosis at 32% for colorectal cancer and thus including thrombocytosis as a criterium in the selection process may lead to earlier diagnosis in a considerable number of patients.

Increasing platelet counts, even at normal levels, is associated with a rising incidence of colorectal cancer in an unselected population [14]. A systematic review of case-control studies found further proof for the relationship between thrombocytosis and all forms of cancer, except breast cancer [5]. Later the same study group showed in a prospective study that patients with thrombocytosis compared to the general population had a higher risk for lung and colorectal cancer in particular, while other cancer forms did not, or even showed an adverse association [6]. Interestingly, the authors of this study note that 1/3 of the patients developing colorectal cancer did not have any other cancer specific symptoms the year before the diagnosis. Thus, to further investigate the risk of thrombocytosis unrelated to other, commonly with colorectal cancer associated symptoms, a prospective study including an unselected Swedish primary care population would be desirable.

Conclusion

With a PPV comparable to those of the other criteria that are included in the Swedish colorectal CPP – rectal bleeding, iron deficiency anemia, rectal exam findings, respectively imaging findings – thrombocytosis may further enhance the process of selecting patients who may benefit from a prioritized referral and fast-track further examination.

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Figures and tables

Figure 1.

Diagram to show the number of patients included, and the number excluded. CPP=cancer patient pathway.

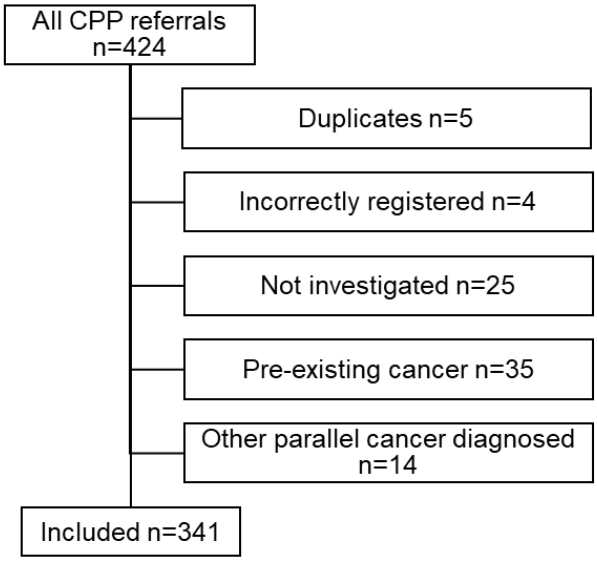

Table 1.

Sample characteristics.

		CRC n=45	No CRC n=296	Total n=341	p-value
Age		72.58 (SD 10.2)	66.10 (SD 13.92)	66.96 (mean SD 13.65)	p=0.003
Gender	Females	23	169	192	p=0.45
	Males	22	127	149	
TPK value		327.76 (SD 190.50)	270.88 (SD 87.08)	278.66 (mean SD 108.60)	cp=0.001 on t-test
Thrombocytosis	Yes	8	17	25	p=0.006
	No	37	267	304	
Assessed as CPP	Yes	44	224	268	p = 0.001
	No	1	72	73	
Rectal bleeding	Yes	17	91	108	p=0.40
	No	13	97	110	
Anemia	Yes	16	63	79	p=0.003
	No	29	233	262	
Rectal exam findings	Yes	13	34	47	p=0.001
	No	17	161	178	
Diagnostic imaging findings	Yes	14	6	20	p=0.000
	No	0	15	15	

Table 2.

Positive and negative predictive values of colorectal cancer for thrombocytosis and the 4 criteria for well-founded suspicion of cancer according to the colorectal CPP.

	PPV	NPV
Thrombocytosis	32%	87.8%
Rectal bleeding	15.7%	88.2%
Anemia	20.3%	88.9%
Rectal exam findings	27.7%	90.4%
Diagnostic imaging findings	70%	–

Table 3.

Crude and adjusted ORs for colorectal cancer.

		Crude OR (95% CI)	Adjusted OR model 1	Adjusted OR model 2
Age groups	0 – 59	Reference	Reference	Reference
	60 – 79	2.54 (CI 1.06 – 6.07)	2.95 (CI 1.20 – 7.75)	1.48 (CI 0.52 – 4.25)
	80 – 100	3.26 (CI 1.21 – 8.79)	3.69 (CI 1.34 – 10.21)	1.78 (CI 0.54 – 5.88)
Gender	Females	Reference		
	Males	1.27 (CI 0.68 – 2.39)		
TPK	Normal	Reference	Reference	Reference
	Increased	3.40 (CI 1.37 – 8.42)	4.06 (CI 1.57 – 10.50)	3.93 (CI 1.16 – 13.39)
Anemia	No	Reference		Reference
	Yes	2.04 (CI 1.04 – 3.99)		2.64 (CI 0.03 – 6.77)
Rectal exam findings	No	Reference		Reference
	Yes	3.62 (CI1.61 – 8.15)		4.48 (CI 1.95 – 11.25)
Rectal bleeding	No	Reference		
	Yes	1.39 (CI 0.64 – 3.03)		

Appendix

Flowchart showing the way of entering the colorectal CCP in Sweden.