“Development of a clinical care pathway for anaemic patients”

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Declaration

I declare that this work has been done and the thesis composed by myself. It is an original piece of work and is submitted in accordance with the requirements of Keele University for the degree of Masters in Philosophy

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Abstract

Improving cancer survival in the UK is one of the leading items on the agenda of the government. Survival from gastrointestinal cancer is yet to come into line with Europe. In 2000 the department of health (DoH) introduced guidelines for referral of patients with suspected cancer. Iron deficiency anaemia (IDA) is one of the criteria for urgent referral for suspected cancer of the upper and lower gastrointestinal tract. The British Society of Gastroenterology (BSG) produced guidance on investigating patients with IDA to ensure identification of sources of occult blood from the GI tract. However due to a lack of clear guidance on how to streamline patients into upper or lower GI investigation pathways has resulted in significant delays. Furthermore there is evidence that there is significant delay in diagnosing proximal colon cancers in patients presenting with anaemia due to time spent in the investigation loop.

A literature review was conducted and this confirms that in patients above the age of 45 with unexplained IDA an upper GI cause is present in 40-60% of patients. Lower GI blood loss accounts for 26 to 31% of causes of anaemia. Colon cancer is the commonest cause with 11% on average for all causes of anaemia.

We also studied the incidence and profiles of anaemia in a cohort of patients with common GI malignancies. The incidence of anaemia that met the DOH and BSG guidance was 22% and 25% respectively.

We identified a potential for blood profiling to help differentiate upper and lower GI malignancies. Proximal colon cancer presented with a higher proportion of patients with anaemia and lower MCV, MCH, MCHC and a higher RDW as compared to upper GI cancers. We also identified a need to reduce the haemoglobin threshold for referral of any patient over the age of 45 with unexplained anaemia.

We conducted a prospective study assessing symptoms and blood profiles of patients referred with anaemia to a dedicated clinic. Using these profiles a scoring tool to predict likelihood of site of cause of anaemia was generated. We confirmed the poor sensitivities and specificities of symptoms for conditions of the GI tract in the presence of anaemia. However symptom combinations improved the sensitivity and specificity for identification of patients at risk of having serious conditions causing anaemia.

The scoring tool combined symptoms and blood profiles to aid in streamlining patients to the appropriate investigation. The tool generated a probability of having a serious condition causing anaemia in the upper or lower GI tracts. The scoring tool had a high discriminatory power with a sensitivity and specificity to GI causes of anaemia better than the current

guidelines. A clinical pathway is proposed where the scoring tool is used to aid in streamlining investigation.

Dedication

I dedicate this work to my wife Helen, who has been a great support in finishing this work.

To my daughters Maymuna, Nafeesa, and Nyila for the time I spent away. “I promise I’ll make it up to you.”

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Chapter 1

Background and review of literature

Introduction

In response to the findings of the EUROCARE[2, 3] study report on survival of cancer, the Department of Health (DoH) and the National Health Service (NHS) introduced initiatives and cancer care plans to improve survival from cancer[4]. The target was by 2010 to reduce mortality of all cancers in patients aged under 75 by 20% in comparison with a 1995-97 baseline[5]. Early referral has a role to play in the improvement of care for people with cancer, and in some cancers early referral may improve survival rates[5]. Primary health care has particular responsibility for the early detection of cancer and the initiation of speedy referral to specialist services. A recent report by the National Audit Office (2004)[6] on cancer services in England observed that patients in England tend to have more advanced cancer at the time of diagnosis than some other countries, particularly in breast and bowel cancer. Delay in diagnosis at primary care could be explained by the failure of some patients to seek help quickly, and by the difficulties general practitioners can face in identifying people with cancer, hence delayed referral. However once the patient is referred further delay could occur awaiting appointment to secondary care, investigation or treatment [7].

The DoH report in 2002, categorized bowel cancer as a major health problem [7]. Bowel cancer 5 year survival is less than 40%. It has considerable burden on the NHS, and individuals suffering with it.

Table 1.1 demonstrates the incidence of selected cancers in UK.

Table 1.1: Newly diagnosed cancers in the UK 2006-2008: selected sites.

Cancer		Gender	Total New Cases p.a.	No p.a. per 100,000 population(95%CI)
Upper GI	Oesophagus	M	5285	14.5(14.3-14.8)
		F	2778	5.6(5.5-5.7)
	Stomach	M	5019	13.2(13.0-13.4)
		F	2777	5.4(5.3-5.5)
	Pancreas	M	3916	10.6(10.4-10.8)
		F	4094	8.3(8.2-8.5)
Lower GI	Colorectal	M	21070	56.7(56.3-57.1)
		F	17211	36.3(36.0-36.6)

Table 1.2: Total deaths from cancer males and females, all ages, UK 2006-2008.

Cancer group	Male	Female
Colorectal cancers	8,489	7,342
Oesophagus	4,900	2,559
Stomach	3,240	1,989

Adapted from Office for National Statistics. Death from cancer: selected sites by gender,2006-2008[8].

DOH guidelines for referral of patient with suspected colon cancer.

Colorectal cancer is the 3rd cause of cancer related deaths in both men and women[8]. The mortality has improved since 1995 with a reduction from 28.2 to 24.9 deaths per 100,000 in males in 2003 and from 18 to 14.5 per 100 000 women in 2003 (Table 1.3)[9].

Table1.3. Death rates from selected cancers: by sex in the United Kingdom.

Rates per 100,000 population					
	Males			***Females***	
	Colon	**Rectosigmoid and Anus**		**Colon**	**Rectosigmoid and Anus**
1995	18.2	10	**1995**	13.1	4.9
1996	17.5	9.9	**1996**	12.6	4.9
1997	17.6	9.3	**1997**	12.2	4.8
1998	16.9	9.5	**1998**	11.7	4.7
1999	16.1	9	**1999**	11.6	4.6
2000	15.8	8.9	**2000**	10.7	4.5
2001	15.6	8.9	**2001**	10.3	4.5
2002	15.1	9.1	**2002**	10.4	4.4
2003	15.7	9.2	**2003**	9.9	4.6

Due to the poor survival compared with Europe and the USA, major reforms in screening and referral of symptomatic patients have been introduced.

There are about 30,000 cases of colorectal cancer per year in England and Wales (3). 99% are aged above 40 years.

To assist primary healthcare professionals identify people with suspected cancer as early as possible, the Department of Health issued guidelines on the topic in 2000[10]. The two week rule and referral guidelines were

introduced to facilitate recognition and streamlining of patients with high risk of cancer. The primary aim was to identify 90% of patients with bowel cancer through this new system [4].

The guidelines are based on high risk symptoms and signs of any abdominal masses and anaemia.

It is recommended that WHEN OCCURRING FOR THE FIRST TIME these symptom and sign combinations should be used to identify patients for urgent referral under the two week standard [4].

- Rectal bleeding WITH a change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks. all ages;
- A definite palpable right-sided abdominal mass, all ages;
- A definite palpable rectal (not pelvic) mass, all ages;
- Rectal bleeding persistently WITHOUT anal symptoms if over 60 yrs;
- Change of bowel habit to looser stools and/or increased frequency of defecation, WITHOUT rectal bleeding and persistent for six weeks, over 60 yrs;
- Iron deficiency anaemia WITHOUT an obvious cause

(Hb < 11 g/dl in men or < 10 g/dl in postmenopausal women).

Under the umbrella of NICE, these guidelines where further revisited by an advisory group in 2002 and report published by the Department of Health

[5]. NICE also analysed the evidence and endorsed the guidelines with an aim for a second consultation [5].

The evidence for the referral guidelines is based on predictive values derived in hospital studies and on the common modes of presentation of established bowel cancer.

The guidelines aimed to prioritise those patients most likely to have cancer so that with existing resources, most will be seen in outpatients within two weeks of referral. The aim is that as the resources for investigation are improved, the criteria for access to the fast-track clinics can be increased and age thresholds lowered so that more patients with lower risk symptoms can be included[5].

The high risk criteria for referral are based on symptoms and signs that are commonly associated with colon cancer[7].

The incidence of primary bowel symptoms varies with site [7, 11, 12]. The mode of presentation for the left and right colon demonstrates clearly separate patterns (Table 1.4). Proximal colon cancer (proximal to sigmoid colon) commonly presents with one of the three cardinal factors: intestinal obstruction, anaemia or an abdominal mass [11, 13, 14]. Nearly a third attends as an emergency [15]. Primary symptoms have been identified in patients with proximal cancer but usually in the presence of the main cardinal features. Primary symptoms exist on their own in only 5%. In

contrast, tumours situated in the descending colon, sigmoid colon or rectum, usually present with distinct primary symptoms [11, 16-18].

Table 1.4: Prevalence of symptoms of colorectal cancer grouped by site [7].

Distal colon cancer		**Proximal colon cancer**	
Rectal bleeding and a change in bowel habit	55-65%	**Anaemia with**	54%
		Primary symptoms	48%
		No primary symptoms	52%
		Abdominal mass	43%
Change in bowel habits alone	20-25%	**Primary symptoms with**	72%
		Anaemia	37%
		Abdominal mass	44%
		Emergency surgery	49%
Rectal bleeding alone	15-20%	**Emergency surgery**	34%
		Primary symptoms on their own	5%

Primary symptoms: Change in bowel habits, Rectal bleeding, Abdominal pain

The DoH referral guidelines have been widely disseminated and implemented. However, accuracy and efficacy remains a concern [19-24]. The poor specificity of the guidelines [24] resulted in an increase number of referrals without increasing the yield of cancer detection. Failure to implement the guidelines accurately has also resulted in further reduction of

cancer detection with a significant number of cancers presenting through routine routes [21, 25].

Although cancer survival is dependent on several factors, as yet there is no evidence to suggest that introduction of current referral guidelines have improved on survival[26].

Hence, improving the specificity and the sensitivity of a risk assessment tool will enable better targeting for assessment of high risk patients to improve delay in diagnosis and shift stage of cancer.

Selvachandran et al [16] improved the sensitivity and specificity of colorectal symptoms and symptom complexes to detect colon cancer by allowing for a score to be generated to stratify risk. This has proven effective in identifying early distal colorectal cancer[27]. The difficulty in achieving an improvement in proximal colorectal cancer detection perhaps lies in the fact that the cardinal symptom of presentation; iron deficiency anaemia (IDA), is non-specific.

However, as IDA provides a portal for detecting proximal colorectal and upper GI malignancies, further emphasis on its value as a high risk criterion is demonstrated by its incorporation in the referral guidelines for suspected bowel and upper GI malignancies [10].

Guidelines for referral of patients with suspected oesophageal or gastric cancer.

In 1997 approx 6,000 oesophageal and 10,000 gastric cancer cases were diagnosed in England and Wales. The incidence of stomach cancer is decreasing, whereas the incidence of oesophageal cancer is increasing. Tumours at the junction between the stomach and oesophagus are increasing particularly rapidly with 99% of cases occurring in patients over 40 years and 90% of gastric cancers occurring in patients over 55 years. [5, 10]

In an attempt to aid identifying patients at high risk of having oesophagogastric cancer the DoH introduced guidance in 2000[10]. This was later reviewed and endorsed by NICE [5].

The Department of health guidance on referral with suspected upper GI cancer:

Referral with in the 2 week rule should be undertaken in any patients with -

• Dysphagia – food sticking on swallowing (any age);

• Dyspepsia at any age combined with one or more of the following 'alarm' symptoms:

- weight loss
- proven anaemia
- vomiting

• Dyspepsia in a patient aged 55 years or more with at least one of the following ‘high risk’ features:

- Onset of dyspepsia for less than one year;
- Continuous symptoms since onset.

• Dyspepsia combined with at least one of the following known risk factors:

- Family history of upper GI cancer in more than 2 first degree relatives
- Barrett’s oesophagus
- Pernicious anaemia
- Peptic ulcer surgery over 20 years ago
- Known dysplasia, atrophic gastritis, intestinal metaplasia

• Jaundice

• Upper abdominal mass

As upper GI cancers are relatively uncommon in primary care and dyspeptic symptoms very common, the chance of a dyspeptic patient under the age of 55 having gastric cancer is extremely low[28, 29]. Dyspepsia is very common in the general population [30] and a poor predictor of cancer[31-33]. Unfortunately the symptoms yielding a higher predictive power for upper GI cancer such as dysphagia, weight loss and anaemia are associated with advanced stage[34].

However the combination of upper GI symptoms has been shown to provide some degree of accuracy in predicting upper GI cancer [31].

In a study by Irving et al[35] the introduction of referral guidelines has improved the delay from first general practitioner consultation to endoscopy, however the stage of cancer did not differ from before introduction of the guidelines.

Anaemia in the presence of dyspeptic symptoms is also reported to increase the risk of presence of upper GI cancer [5]. Anaemia is a more common presentation in gastric cancer (22%) than in oesophageal cancer (5.5%)[36]. Nevertheless, as anaemia is a mode of presentation of both upper and lower GI cancers then the investigation of patients over the age of 45 presenting with unexplained anaemia needs to be targeted to rule out cancer as a priority.

Iron deficiency anaemia and investigation in secondary care.

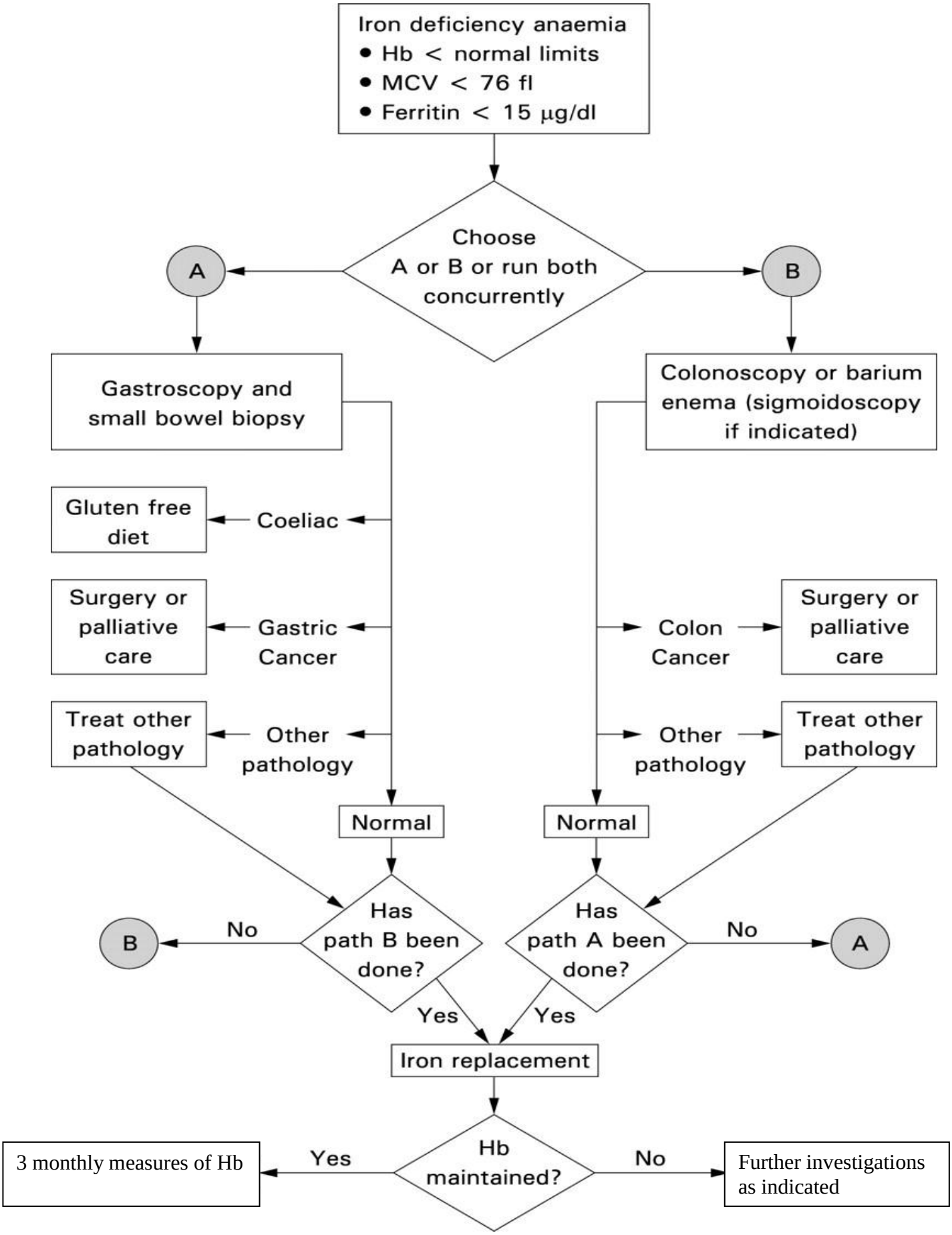
IDA occurs in 2–5% of adult men and post-menopausal women in the developed world and is a common cause of referral to a gastroenterology clinic (4–13% of referrals)[37]. While menstrual blood loss is the commonest cause of IDA in pre-menopausal women, blood loss from the gastrointestinal (GI) tract is the commonest cause in adult men and post-menopausal women [38-41]. Asymptomatic colonic and gastric carcinoma may present with IDA

and exclusion of these conditions is of prime concern. The management of IDA is often suboptimal with most patients being incompletely investigated, if at all [42].

The British Society of Gastroenterology (BSG) published its guidelines for the investigation of IDA in 2000[1]. Although guidelines where based on relatively weak evidence they have been accepted widely [1]. It has been reported that since these guidelines have been published there has been an increase in the identification of GI malignancies [43-46]. However, benefit in detecting early cancer remains to be demonstrated.

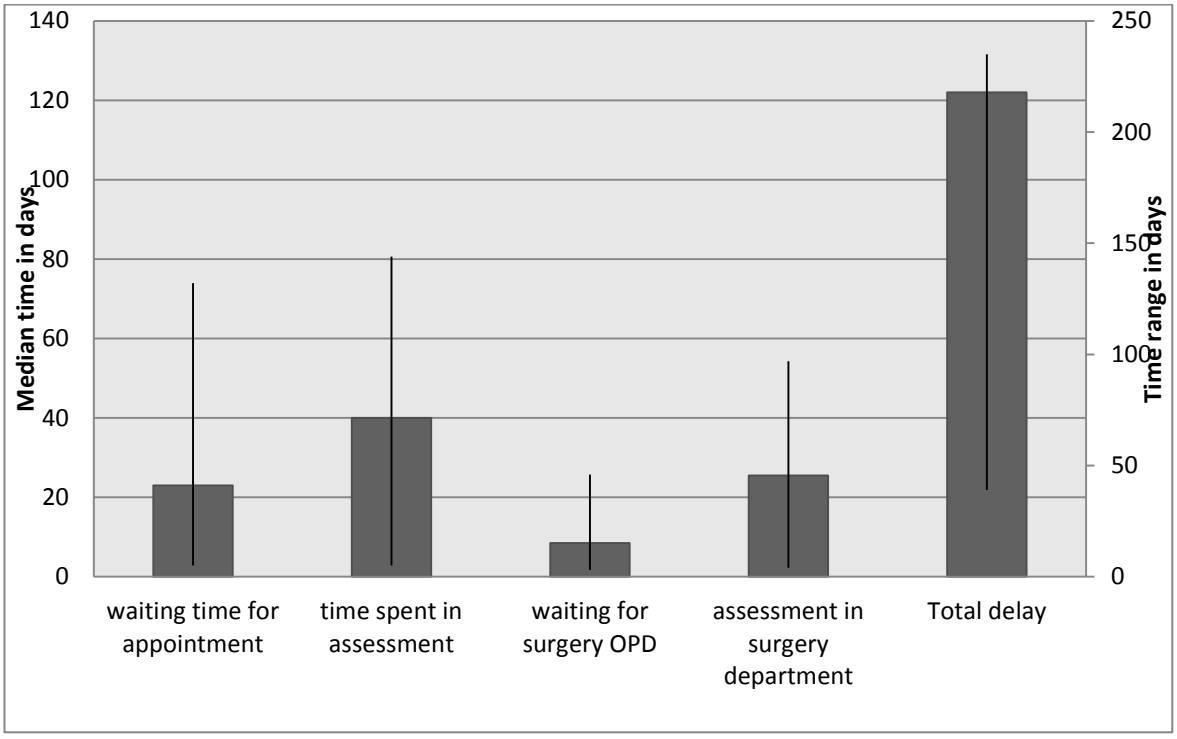
Several issues have been highlighted by the BSG, DoH and NICE guidelines. These include the high incidence of IDA and its effect on resources; the high threshold of anaemia which directs investigation of IDA; and the value of investigating those with non-iron deficiency anaemia. These issues are yet to be clarified [1, 5, 10]. Although the DoH guidelines stipulate early referral of patients with IDA to secondary care, there is no clear guidance on how secondary care should manage this cohort. The BSG guidelines (Figure 1.1) have not clearly identified criteria for investigation selection following referral to secondary care. Further clarification is necessary and criteria for selection are needed to prevent delay in reaching the possible diagnosis especially where there are long delays awaiting further investigations.

Figure 1.1 The BSG guidelines for investigation of patients with IDA[1]



In a study conducted at Leighton hospital, 62 patients who were diagnosed with proximal cancer from 1998 to 2001 where analysed. Timeline and process of investigation from referral to treatment as well as final stage of cancer was studied. We demonstrated a delay in patients presenting with proximal colon cancer (PCC) whilst being investigated in hospital [47] (figure 1.2).

Figure 1.2: Median delay in days of care pathway of proximal colon cancer patients.



(Bar represents median, vertical line represent range (min-max))

This total time to treatment was higher in anaemic PCC patients although this did not reach statistical significance (*p=0.6* Mann-Whitney U test). There was, however, no difference in the proportion of anaemic patients between stages of cancer at presentation (*p=0.8* chi-square test), (Table 1.5)

confirming that anaemia remains a predominant feature of proximal colonic cancer regardless of stage.

Table 1.5: Total time in days from referral to treatment of PCC patients and stage of cancer.

	Median in days (95%CI)	Dukes B	Dukes C	Dukes D
Anaemic	55(23-85)	74%	67%	78%
Non-Anaemic	30(16-118)	26%	33%	22%

Anaemia and blood indices.

Anaemia is defined as total haemoglobin (Hb) level below the lower limit of normal reference range , although the standards can differ from one laboratory to the other it is commonly accepted that Hb less than 13grams/ dl for men and 11.5grams/dl for women constitutes anaemia.[48]

Anaemia can be classified according to cause or morphology.

Classification according to cause will provide a useful blueprint for the basis of our hypothesis in later chapters.

Hence we can group classify acquired causes of anaemia into:

a. Decreased production of red blood cells or Hb.

   This could be due to deficiency in nutrients essential in Hb and red cell production for example iron, vitamin B12 and folic acid or toxicity of

bone marrow resulting in reduction of bone marrow red cell precursors such as that seen in bone marrow replacement with malignant cells (primary or metastatsic) or para-neoplastic supression. In anaemia of chronic disease Hb production is restricted due to relative iron deficient erythropoiesis due diversion of iron to inflammatory response .

b. Increased destruction of red blood cells.

   This a state where there is loss of red cells due to excessive destruction, e.g. haemolytic anaemia, spherocytosis or acute loss such as bleeding.

Deficiency of the essential nutrient Iron is relevant to this study and hence we will discuss this further.

In Iron deficiency there is impairment in the production of Hb as Iron is the precursor of the heme molecule. Deficiency of iron does not impair the production of red blood cells, except when severe deficiency occurs where reduction in red blood cell precursor proliferation occurs. Hence this will result in circulating red blood cells having less haemoglobin causing a reduction in size and colour (microcytic hypochromic anaemia).

Iron ions circulate bound to plasma transferrin and accumulate within cells in the form of ferritin. They serve as an enzyme cofactor and oxygen carrier [49].

Adult men normally have 35 to 45 mg of iron per kilogram of body weight [49]. Levels are lower in premenopausal women as a result of recurrent blood loss through menstruation. The majority of iron is incorporated into haemoglobin in developing erythroid precursors and mature red cells. Intestinal absorption of iron occurs via the duodenal crypt cells. They sense the iron requirements of the body and are programmed by that information as they mature into absorptive enterocytes [49]. Enterocytes lining the absorptive villi close to the gastroduodenal junction are responsible for all iron absorption. A combination of low pH of gastric effluent and reduction of ferric iron to ferrous form by brush-border ferrireductase facilitates absorption [49]. Heme iron is taken up by a separate process that is not well characterised. Heme iron is absorbed more efficiently than inorganic iron by the human intestine [50]. Heme enters the enterocyte as an intact metalloporphyrin[51]. The absorption of intestinal iron is regulated in several ways:

a. Dietary regulation: based on iron recently consumed in diet which causes enterocyte saturation with iron.

b. Store regulation: This is dependent on iron levels and responds to total body iron.

c. Erythropoietic regulator: Iron absorption changes in response to the requirements for erythropoiesis. This regulator has a greater capacity

to increase iron absorption than the stores regulator[49]. The mechanism of how this control is achieved is unknown.

Haemoglobin production is untroubled until iron stores are depleted, as reflected by low serum ferritin levels[49] . This results in iron deficient erythropoiesis when the stores have been used up, and the iron saturation of transferrin decreases[52]. There is also a rise in free protoporphyrin in red cells. The levels of soluble transferrin receptor, a protein-cleavage product that is present in plasma, increase when iron deficiency limits the production of new red cells. Anaemia with microcytosis is the last event (Table1.6).

A decreased reticulocyte Hb level is a useful early indicator of iron-deficient erythropoiesis and may be superior to other laboratory measures in this respect [53].

Anaemia of chronic inflammation, also known as anaemia of chronic disease, has some features in common with IDA. Iron-deficient erythropoiesis results from a defect in iron recycling. Reticuloendothelial iron stores are high in macrophages, but this iron is not available to erythrogenesis. Laboratory findings may include low serum iron levels, low serum iron-binding capacity, increased serum ferritin, and normocytic or slightly microcytic erythrocytes. In contrast to patients with IDA, those with anaemia of chronic inflammation do not have elevated levels of serum transferrin receptor [54] (Table 1.6).

Table 1.6 Phases of iron deficient anaemia and corresponding blood indices. [48]

Iron stores	Normal	Storage- iron depletion	Iron-deficient erythropoiesis	Iron-deficient anaemia
Reticulo-Endothelial marrow iron	Present	Trace/absent	Absent	Absent
Serum Ferritin(µg/l)	15-300	20	10	<10
Serum Iron(µmol/l)	10-30	20	<10	<7
Transferrin receptor(mg/l)	2.8-8.5	<8.5	>8.5	>8.5
Marrow sideroblasts (%)	30-50	30-50	<10	<10
Red cell Protoporphyrin (µmole/mol hb)	<80	<80	>80	>80
Red cell production				
Haemoglobin (g/l)	Normal for Lab reference	Normal for Lab reference	Normal for Lab reference	< Normal for Lab reference
MCV (fl)	80-92	80-92	80	<80
MCH (g/l)	27-32	27-32	27	<27
Morphology	Normal	Normal	Normal	Microcytic Hypochromic

It is hypothesised that chronic inflammation processes result in withholding iron from microbes as well as from erythroid precursors[55]. Mild anaemia may be a relatively small price to pay for the attenuation of infection. Hence the only effective treatment for anaemia of chronic inflammation is correction of the underlying disorder.

Blood Indices.[56]

A routine full blood count (FBC) will assess red blood cells and their indices, white blood cells and platelets.

Blood indices are:

a. Measured indices: Hematocrit, Haemoglobin levels, Red blood cell count and Red distribution width, or
b. Calculated: these are calculated from the above indices. They include Mean corpuscular volume, Mean corpuscular haemoglobin, Mean corpuscular haemoglobin concentration.

The haematocrit is a measure of the total volume percent formed by the red blood cells in a sample of whole blood, also known as packed cell volume.

The haemoglobin is a measure of how much haemoglobin protein is in the blood, expressed in grams/dl.

The red blood cell count (RBC) measures the number of red blood cells present in the unit of whole blood volume, expressed in number x 10^9 cells/ml.

The relationships between the hematocrit, the Hb level, and the RBC are converted to red blood cell indices through mathematical formulas. These formulas were worked out and first applied to the classification of anaemia by Maxwell Wintrobe in 1934[48].

Mean corpuscular volume (MCV)

MCV is the index most often used. It measures the average volume of a red blood cell by dividing the hematocrit by the RBC. The MCV categorises red blood cells by size. Cells of normal size (80-92 fl) are normocytic, smaller cells are microcytic(<80fl) and larger cells are macrocytic(>92fl). These size categories can be used to classify anaemia too.

Mean corpuscular haemoglobin concentration (MCHC)

The MCHC measures the average concentration of Hb in a red blood cell. This index is calculated by dividing the Hb by the hematocrit. The MCHC categorises red blood cells according to their concentration of haemoglobin. Cells with a normal concentration of Hb are called normochromic; and cells with a lower than normal concentrations are called hypochromic. Because there is a physical limit to the amount of Hb that can fit in a cell, there is no hyperchromic category.

Just as MCV relates to the size of the cells, MCHC relates to the colour of the cells. Haemoglobin contains iron, which gives blood its characteristic red colour.

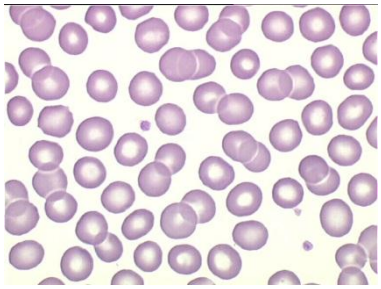
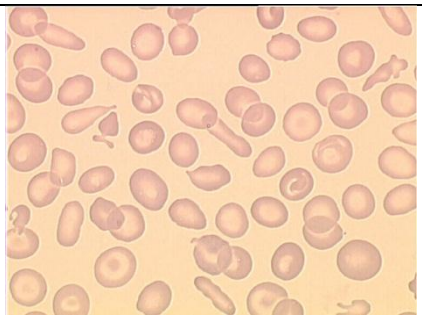
Mean corpuscular haemoglobin (MCH)

The average weight of Hb in a red blood cell is measured by the MCH. The formula for this index is Hb multiplied by 10 and divided by the RBC. MCH values usually rise or fall as the MCV is increased or decreased.

Red cell distribution width (RDW)

The RDW measures the variation in size of the red blood cells. Usually red blood cells are a standard size. Certain disorders such as IDA, however, cause a significant variation in cell size. It is also a reflection of heterogeneity of the population of blood cells. It is the equivalent of the microscopic description of poikilocytosis.

Figure 1.3 Blood films appearance of poikilocytosis

	
Normal Blood Film	***Poikilocytosis and hypochromia***

Conditions that cause microcytosis could be differentiated using RDW. In IDA the RDW rises due deficient erythropoiesis, however in thalassemia the RBC population is small but homogenous hence the RDW is relatively lower than in IDA.

The haemoglobin and MCV definition of anaemia and IDA have been adapted by the DoH and the BSG. Table 1.7 details the definitions of different criteria.

Table 1.7 Criteria used for classification of anaemia for referral

Criteria for classifying anaemia	Definition
i. Anaemia as per laboratory normal value	Hb <13 in males, Hb<11.5 in females
ii. Microcytosis as per laboratory normal	MCV< 82 in males, MCV < 78 in females
iii. Local definition of IDA	Anaemia and Microcytosis as per laboratory limits
iv. Anaemia as per DoH referral criteria	Hb <11 in males, Hb <10 in females
v. DoH Criteria for Iron Deficiency Anaemia	Anaemia as defined by DoH criteria and MCV<76
vi. BSG criteria for IDA	Hb less than normal for laboratory and MCV <76 or Ferritin < 15

Review of common GI pathologies causing anaemia

Abstract

Iron deficiency anaemia (IDA) in the over 45 year olds is commonly caused by occult gastrointestinal (GI) blood loss. It is thus recommended to evaluate the GI tract as a priority. Pathology identified on investigation of the upper and lower GI tract vary in incidence in this population. This review aims to evaluate the literature with respect to common causes of chronic blood loss identified during the investigation of patients over 45 presenting with IDA. A PubMed search using: anaemia, iron deficiency, gastrointestinal, endoscopy, was conducted. Prospective studies reported in the English language were retrieved. A further cross reference of bibliography of the selected papers and major guidelines papers was conducted to retrieve further studies. A total of 18 studies were identified and reviewed. Upper gastrointestinal loss is the commonest cause of IDA, accounting for 12-70% of all causes. Inflammatory gastritis is the leading cause in the upper GI and overall causes of IDA. Gastric and oesophageal cancers are rare causes, (less than 8%). Lower GI causes account for 9-56% in all the reports. Colon cancer is the leading cause in the lower GI tract and the commonest malignancy causing IDA. The incidence increases with age. Pathologies such as hiatus hernia,

diverticular disease should be accepted as causes only if all other causes excluded and are clinically severe.

Introduction

Occult GI blood loss remains the commonest cause of IDA in those over 45years old[57]. GI investigation identifies a potential source of bleeding in up to 85% of the cases [57]. However, the reports vary in what they accept as a potential cause of anaemia as some of the described pathologies are prevalent in the general population[58].

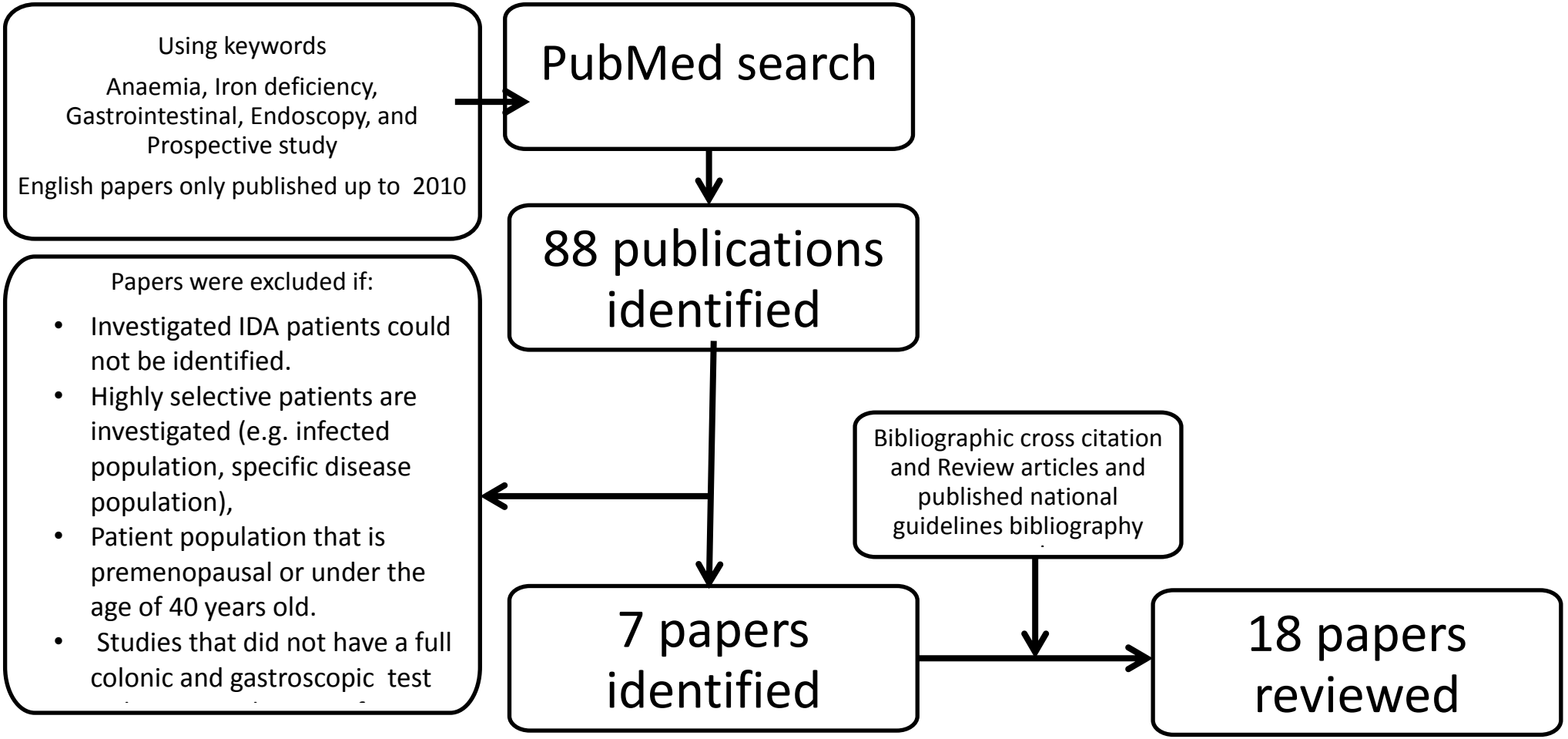
This section reviews the literature for studies that reported GI causes of anaemia, exploring the relationship between commonly reported pathologies and occult GI blood loss.

Methods

The review aimed to identify all studies that evaluated patients who presented with iron deficiency anaemia and have been assessed at with dual upper and lower gastrointestinal investigation as a minimum.

Search of the PubMed Medline (US National Library of Medicine) was conducted using the key words: anaemia, iron deficiency, gastrointestinal, endoscopy, and prospective. Only English language papers were selected with a publication date up to 2010(Figure 1.4). This search returned a total of 88 papers.

Figure 1.4: Literature review search flow diagram



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Abstracts of the publications were screened independently by two reviewers for relevant studies. Exclusion criteria were as follows:

- Investigated IDA patients could not be separated from the total sample;
- Highly selective patients are investigated (e.g. infected population, specific disease population);
- Patient population that is premenopausal or under the age of 40 years old;
- Studies that did not have a full colonic and gastroscopic evaluation;
- Failure to describe, or absence of, diagnoses in detail.

7 publications were identified from the search. The bibliographies of the selected publications were then screened for relevant cross citations and retrieved. Furthermore, bibliography of recent review articles and national guidelines on investigation of iron deficiency anaemia were also screened for relevant papers. An additional 11 publications were identified and included in the review. A total of 18 publications were analysed.

Quality appraisal: All studies were prospective. The population characteristics were clearly defined. However some papers were included in spite of these potential biases:

- McIntyre et al[37] 93 out of the 111 patients had complete upper and lower GI investigation;

- In Landy et al's study[59] the authors reported only predefined diagnosis;
- Nahon et al had a female only population[60];
- Urquhart et al[61] had 5% of the population under the age of 40 and did not list the diagnosis in 16% of the upper GI causes and 11% of he lower GI causes;
- Annibale et al[62] had an unknown proportion aged < 40 years;
- In Joosten et al[63] the population was elderly (>70 years);
- Urquhart et al [61] and Landy et al [59] had retrospectively analysed prospectively collected data.

Results

The findings of upper and lower GI investigation were summarised in tables 1.8, 1.9 and appendix 1.

Upper Gastrointestinal Tract

The upper GI tract is the commonest site where a cause of anaemia is identified. The incidence ranges from 12-70% in 18 studies reviewed. The BSG guidelines reported a 30-50% rate for detection of cause of IDA in the upper GI tract[1]. Gastric or duodenal ulcers are the commonest cause of anaemia in the upper GI tract, accounting for 7 to 51% of all upper GI causes and 2-26% of all causes of IDA . It is also the commonest diagnosis in all patients investigated for anaemia (Table 1.8 and 1.9).

Table 1.8: Publications reporting diagnosis of causes of iron deficiency anaemia in patients who had upper and lower gastrointestinal evaluation.

Study	Annibale	Bampton	Capurso	Coban	Cook	Gordon	Hardwic	Joosten	Kepczyk	Landy	McIntyre	Nahon	Niv	Park	Rockey	Sari	Urquhart	Zuckerman
No of patients with Anaemia	**71**	**80**	**98**	**96**	**100**	**170**	**89**	**96**	**70**	**478**	**111**	**117**	**48**	**749**	**100**	**95**	**6538**	**100**
Total No of patients with Upper GI causes	**14**	**38**	**20**	**55**	**60**	**70**	**51**	**47**	**39**	**56**	**45**	**54**	**14**		**37**	**55**	**918**	**36**
Gastric or Duodenal Ulcer	7	8	9	25	8	15	10	12	6	17	23	9	1	71	19	23	377	7
Gastric Cancer	2	1	5	6	5		7	2	3	10	8	7	2	14	1	7	22	1
Gastritis (inflammatory or atrophic)	19	2	14	12	14	7		17	11		7	17	9	16	6	16		12
Oesophagitis		14		11	14	8	26	12	10	4	15	9	2	1	6	7		6
Celiac disease	4		11			3	2		4		3					2		
Gastric Venous Malformation		1			5			6	4	12		3			3		231	8
Gastric or duodenal polyps		6		3				4	2			6		1	1			1
Oesophageal Cancer				1	1		2		1									
large Hiatus Hernia or with erosions	5	2	7		7								2					
Oesophageal Varices					3													2
Duodenitis													1					2
***H pylori* Gastritis**	13		15															
Other upper GI causes		5	5		10	6	6		2	21	4				1		493	
Total No of patients with Lower GI Causes	**18**	**16**	**27**	**26**	**23**	**30**	**50**	**31**	**21**	**55**	**18**	**31**	**16**		**26**	**10**	**586**	**26**
Colonic Vascular Malformation	3	1	4	2	2	3	2	6	6	11	1	5	3	3	5		251	5
Colon Cancer	10	7	13	8	14	9	33	13	4	24	5	14	11	25	11	5	116	6
Colonic Polyp	2	5	4	3	6		8	10	7	18	8	10	5	21	5	1	409	14
All Inflammatory Bowel Disease	1	1	1	2	3	4	9	1	1	9	2			9	2	1		
Colonic Ulcers															2			2
Piles				6				1	4					25		3		
Severe Diverticular Disease			5	3														
other colonic causes							1				3			8	1			
Dual pathology	**4**	**5**		**1**	**12**		**26**		**12**	**7**	**2**		**3**		**1**			**9**

Table 1.9: Literature review summary of incidence of causes of anaemia on endoscopic evaluation of the gastrointestinal tract as investigation for iron deficiency anaemia

	Number of studies	Combined total number of patients from all studies	Range of number of patients with diagnosis	Range of incidence of diagnosis in anaemic patients (%)	Range of incidence of diagnosis in respective site of GI tract (%)
No of patients with Anaemia	***18***	**9206**	**48-6538**		
No of patients with Upper GI causes	***17***	**1645**	**14-918**	**12-70**	
Gastric or Duodenal Ulcer	***18***	647	1-377	2-26	7-51
Gastric Cancer	***17***	103	1-22	0.3-8	2-25
Gastritis (inflammatory or atrophic)	***15***	179	2-19	2-27	5-70
Oesophagitis	***15***	145	1-26	0.1-29	7-51
Celiac disease	***7***	29	2-11	2-11	4-55
Gastric Venous Malformation	***9***	273	1-231	1-8	3-25
Gastric or duodenal polyps	***8***	24	1-6	0.1-8	3-16
Oesophageal Cancer	***4***	5	1-2	1-2	2-4
large Hiatus Hernia or with erosions	***5***	23	2-7	3-7	5-35
Oesophageal Varices	***2***	5	2-3	2-3	5-6
Duodenitis	***2***	3	1-2	2-2	6-7
H pylori Gastritis	***2***	28	13-15	15-18	26-75
Other upper GI causes	***10***	553	1-493	1	3-54
No of patients with Lower GI Causes	***17***	**1010**	**10-586**	**9-56**	
Colonic Vascular Malformation	***17***	313	1-251	0.4-9	4-43
Colon Cancer	***18***	328	4-116	2-37	19-69
Colonic Polyp	***17***	536	1-409	1-14	10-70
All Inflammatory Bowel Disease	***14***	46	1-9	1-10	3-18
Colonic Ulcers	***2***	4	2-2	2	8-8
Piles	***5***	39	1-25	1-6	3-30
Severe Diverticular Disease	**2**	8	3-5	3-5	12-19
other colonic causes	**4**	13	1-8	1-3	2-17
Dual pathology	**11**	**82**	**1-26**	**1-29**	

30

Oesophagitis accounts for 12% [37, 39-41, 64-66] of all causes of anaemia and 26% of all upper GI causes in investigated patients. Hiatus hernia is the commonest upper endoscopic finding in a symptomatic population investigated by means of an upper GI endoscopy [67, 68]. The incidence ranges from 4% to 28%. Hiatus hernia has been reported as a cause of IDA in 7% [39, 57] of patients investigated with dual endoscopy and 11% of all upper GI causes of IDA (Table 1.9). Anaemia will be present in a subset of patients with hiatus hernias [69]. However it is not a common cause of upper GI occult blood loss, unless there are erosions or ulcers[57]. The resultant oesophagitis and or Barrett's metaplasia are other mechanism explaining chronic blood loss. Cameron identified IDA in 6.9% of patients with diaphragmatic hernia [70]. In 41% of patients with anaemia and a large hiatal hernia there are associated linear mucosal erosions at the hiatus from chronic irritation at the diaphragm, commonly referred to as Cameron lesions [71]. In most patients with diaphragmatic hernia and associated anaemia refractory to medical treatment, surgical repair can result in successful resolution of the anaemia [72]. When a large hiatus hernia was identified, it was not the sole factor potentially causing upper GI loss [39]. Cook et al reported that in 5 out of 7 large hiatus hernias, another concomitant upper GI pathology causing anaemia was identified.

Hence hiatus hernia will cause occult upper GI blood loss only if complicated with ulcers or erosions. In contrast, large hiatus hernia causing IDA was the sole finding in 38 patients investigated for chronic blood loss [73]. Cameron lesions were only identified in 50% of these patients. The authors hence concluded that the presence of a large hiatus hernia was enough to cause chronic blood loss.

Gastric and oesophageal cancer are rare, although in patients investigated for anaemia the incidence is higher than the general population, but they only account for 2 to 8 % of causes[31, 74](table 1.9). Oesophageal cancer rarely presents with anaemia and hence the majority of upper GI cancers presenting with anaemia are gastric (1-2% vs.0.3 to 8% respectively)(table1.9). This is to be expected as before oesophageal cancer causes significant blood loss it usually causes obstructive symptoms.

Overall in the upper GI tract inflammatory processes (gastritis, oesophagitis and duodenitis), cancer, polyps and vascular lesions account for the majority of causes, while hiatus hernia in the absence of erosions rarely causes anaemia.

Lower Gastrointestinal Tract

Lower GI blood loss accounts for 9 to 56% of causes of anaemia (table 1.9). Colon cancer is the commonest cause of anaemia in the lower GI tract [57, 64, 75]. It represents on average 38% of all lower GI causes and 11% for all causes of anaemia in investigated patients,(ranges from 2% to 37%)(table1.8,1.9). The majority of these cancers are proximal to the splenic flexure [11]. None of the proximal colon cancers in a cohort of patients studied by Hodder et al had dukes A [47]. In the elderly (>65years old), the colon cancer risk increases significantly. Coban et al have identified colon cancer as the most common lesion in the lower GI tract and the second commonest cause of anaemia in the entire GI tract after inflammatory gastritis[76]. Colonic polyps constitute the second commonest cause (10-70% of lower GI causes and 1-14% of all causes) followed by vascular malformation and inflammatory bowel disease (table1.9).

Diverticular disease has not been commonly recognised as a source of chronic blood loss[77].Two reports(Coban et al[76] and Capurso et al[78]) identified diverticular disease without acute bleeding as a cause of chronic blood loss. Coban et al did not describe the characteristics of the diverticular disease or the severity. Capurso et al, on the other hand, have attributed IDA to diverticular disease only in the presence of

positive FOB. Rupture of the vase recta within diverticular disease is the commonest cause of bleeding acutely [79], but it is not entirely clear how this phenomenon could cause chronic blood loss.

Haemorrhoidal disease is only reported as a cause in one study[65]. Significant chronic blood loss from large haemorrhoid tends to be brought to medical attention.

In summary colon cancer, polyps, inflammatory bowel disease, angiodysplasia and mucosal ulcerations should be regarded as causes of chronic blood loss from the lower GI tract.

Chapter 2

Developing prioritisation tools

Developing prioritisation tools

Abstract

Clinical prediction models are used commonly in medicine. They help identify risk, prioritise tests and target interventions in high risk groups. This chapter discusses fundamental elements in development of clinical prioritisation tools used to streamline tests. These elements consist of a clear definition of the problem in question, the factors that help predict the outcomes and their interactions. Different statistical methods and models are used to generate tools to use in practice to test efficacy and translate some of the statistical measurements into practice.

Introduction

Health care is at the top of the political agenda and the DoH is currently under pressure to meet targets to improve the quality and quantity of care delivery, within the confines of a budget.

Guidelines, prioritisation tools and demand management protocols have been introduced to resolve areas of deficiencies in health care. Ultimately these tools are aiming to improve quality of health care provision and where applicable improve on the outcomes of health problems (e.g. survival in cancer, quality of life in joint surgery and cataract).

The NHS modernisation agency declared core values in the demand management protocols. [NHS modernisation agency, http://www.natpact.nhs.uk/demand_management]

- Individuality: Services will be tailored to each individual's needs in relation to the type, time and location of the service.
- Transparency: All decisions concerning care provision will be open and transparent.
- Evidence: Decisions concerning care will be based, wherever possible, upon evidence, and if this is not possible consensus.
- Equity: Services will be provided in an equitable manner.

Expenditure on healthcare is not a “bottomless pit” and choices have to be made in all medical systems. High demand can cause delay and jeopardise the health of individuals who most need help. It is thus appropriate to prioritise those individuals with the greatest risk and/or disability and also provide a mechanism for equitable and consistent decision making and access.

A balance is necessary to optimise the delivery of health care. Rationalisation of health delivery is a difficult issue that raises debate among patients and health providers. This is an arena for major conflicts. Hence prioritisation tools have a very important role to play if we are to

reduce these possibilities and at the same time make best use of resources.

This chapter highlights essential concepts in developing such tools. Although these appear to be obvious it is surprising how many current guidelines have overlooked these fundamentals. The core structure of these basics revolves on evidence based practice. When adhered to accurately, not only will it result in efficacy of health care delivery but it will also provide a well-controlled source of reliable evidence.

The development of a demand management tool can be summarised in the following steps:

1. Defining the structure of the tool;

2. Testing the tool.

Defining the Structure of the Tool

A) Defining the outcome

The outcome is the dependent factor. It is a product of the interaction of several independent factors.

Defining the outcome involves defining what is to be measured, the relationship between priority and what is measured, and defining the scale used to determine priority.

The outcome is the reason that we need a priority tool. This could reflect symptom severity, quality of life, cancer risk etc.

Priority and outcome measures can be related directly or indirectly. For example in cancer referrals using a risk prediction tool that produces an inference of the chance of cancer will determine priority on a direct relationship with outcome (cancer risk). On the other hand, in hip surgery referrals using a tool that reflects quality of life will determine priority based on lifestyle restriction, not actual hip movement restriction. This is an indirect relationship as other factors could contribute to poor quality of life.

Priority could be reported on a categorical scale; binary (e.g. high and low risk); discrete multiple (e.g. urgent, soon, routine); or continuous scale (e.g. symptom severity score, pain scores etc).

For a tool to be efficient the outcome measure should be:

i. A true reflection of an individual's main concern e.g. symptom severity in cataract, cancer risk in colorectal referrals, likelihood of proceeding and benefiting from surgery in hip and knee replacement.
ii. If the intervention causes a change then this change must be able to be audited e.g. quality of life after joint replacement.

B) Identifying predictors

These are independent factors that have a direct relationship with the intended outcome.

They are the components of the tool. Their power of prediction is dependent on the extent of their relationship, and this can be assessed statistically by means of uni-variant or multi-variant analysis. It is important to recognise inter-relationships between independent variables. Failure to recognise mutually exclusive factors will result in duplication in the prediction module, rendering it complex and not adding to its power.

C) Defining the relationship

When independent factors are used to predict an outcome their relationship can be defined in the form of a mathematical model. The risk factors could simply predict out come in a 1:1 ratio, i.e. if one factor is present regardless of the presence of any other factor then risk is present. A good example is the DoH colorectal guidelines for referral to secondary care which classifies an individual at high risk for cancer (dependent variable “outcome”) if one of several risk factors (independent factors) are present. Such a simple expression of relationship of risk factors rules out the cumulative risk from several factors existing simultaneously. In such circumstances it is preferable to have a model that allows a cumulative build-up of risk, benefit or disability e.g. Selva Score for colorectal cancer risk[16, 80]. The result of

such a tool would be on a continuous scale which allows an accurate assessment of likelihood of occurrence of the outcome. Furthermore continuous scales allow for threshold adjustments to meet available resources.

The relationship between each independent variable and the dependent outcome is not always uniform across the range. Some independent factors have a higher power of association than others. This can be expressed in the form of weightage.

Weights to risk factors can be assigned from likelihood ratios, odds ratios, relative risks. It can also be derived from multivariate analysis e.g. regression analysis.

When the relationship cannot be defined in an objective manner, e.g. patient's preference, then a utility value can be assigned. This is a weight of preference that is determined arbitrarily by consensus of the investigators.

D) Statistical tools

Careful selection of statistical tools is essential in assessing the interaction of dependent and independent factors.

Choice of tool is based on several factors.

i. Uni-variant analysis is used when assessing the interaction between one dependent and independent factor. e.g. t-test, chi-square test, likelihood ratios, odds ratios and relative risks.

ii. Multi-variant analysis is used when assessing the interaction between more than one independent and or dependent variables. Examples of such tools are multiple regression, logistic regression, factor analysis and discriminate analyses

iii. Neural networks.

Conventional mathematical tools define interaction and fit them to a hypothetical line. The majority of the time these are linear relationships. Advanced tools such as polynomial regression fit multiple linear relationships in succession to produce curved relationships. It is apparent that this is not possible all the time.

New computer technologies have developed neural networks that allow for description of interactions in a non-linear form. This has been introduced in medical science to identify relationships in a supervised fashion, i.e. the outcome is known; or unsupervised fashion, i.e. the outcome is unknown.

Although powerful they need training and must not be abused as data mining tools as not all relationships are meaningful[81, 82].

Implementation

The efficacy and performance of any tool not only depends on its intrinsic characteristics but also on its implementation. Production of a tool that is not easily implementable will render it ineffective and incapable of achieving its main goal. It should have a mechanism that transmits the true distribution of risk factors independent of confounding factors.

Considering this at the early stage in development allows us to choose between alternatives in the factors in the tool which will make it easier to use and apply.

In summary an ideal tool must be practical and easy to implement, constructed with inclusion of accurate and powerful predictors of outcome expressed in a model that allows a cumulative assignment of risk and gives each risk factor a weight in proportion to it is power of relationship to the outcome.

Testing the Efficacy

In health research the efficacy of a testing tool for decision making is determined by accuracy indices. These are defined as:

1. Sensitivity: how good is a test in detecting the disease in the diseased population?
2. Specificity: how accurate is the test in correctly identifying those with no disease in the healthy population?
3. Positive predictive value: how accurate is a positive test result? i.e. how many of those who have a positive test have the disease.

Table 2.1 Calculation of sensitivity and specificity

Test	Disease present	Disease absent
Positive	A	B
Negative	C	D

Sensitivity = a / (a+c)
Specificity = d / (b+d)
Positive Predictive value= a / (a+b)
Total positive rate = (a+b) / Total

1- Sensitivity:

The first step in evaluating the efficacy of a prioritisation mechanism is to see if it has met the minimum accuracy in detecting those who would be most likely to benefit (sensitivity). When developing the tool a minimum sensitivity needs to be determined, i.e. we should determine the maximum tolerable

proportion of individuals who are true beneficiaries from the prioritisation tool but have been missed i.e. minimum acceptable or unavoidable failure.

For example, in colorectal referrals, the minimum set sensitivity is 90%. This means that 90 % of the patients who have cancer must be prioritised correctly using any tool; i.e. the maximum tolerable proportion of patients with cancer that are missed is 10%.

A prioritisation tool that is unable to meet the set standard of sensitivity automatically should fail.

In circumstances where sensitivity is not known, then a consensus that sensitivity should be decided on by extrapolation from other targets or prevalence of disease. It could be determined from pilot observational studies in real or virtual environments with set gold standards.

Having a set sensitivity is vital for assessing performance of a tool and essential in a systematic comparison of other tools.

2- Specificity and Management of Demand

Specificity is the main indicator of the effectiveness of demand management.

When prioritising a population; the higher the specificity of the tool, the higher the proportion of those who are true beneficiaries will be - achieving the highest efficiency of the tool.

Provided that a tool achieved the minimum acceptable sensitivity then it could be preferred over others if it has a better specificity - in keeping with the concept of demand management.

The relationship between these factors determines the strength of a testing tool.

The sensitivity and specificity are not the only important factors affecting this relationship. The prevalence of the disease in the population is an important factor in determining how a test can perform. The holistic interaction can be described in the form of the Bayes' theorem:

$$\textbf{Probability of a patient with a positive result having disease} = \frac{\text{Sensitivity x Disease prevalence}}{\text{(Sensitivity x Disease prevalence) +[(1-Specificty) x (1-Disease incidence)]}}$$

The denominator can be converted to the total positive rate of a test (prevalence of a positive test in the tested population). Thus the final equation would then be:

$$\textbf{Probability of a patient with a positive result having disease} = \frac{\text{Sensitivity x Disease prevalence}}{\text{Total Positive rate}}$$

Demand management can be defined in a similar context.

The prevalence of a specific health problem in the population could be the prevalence of "disease". Sensitivity would then be the efficacy of a tool which categorises those who have "disease" and would be in a position to benefit. Specificity would then be the efficacy of the tool to eliminate those who were falsely categorised as being able to benefit. Total Positive Rate would be the total of the population classified as "important" (truly and falsely) i.e. the demand created by the prioritisation tool. The positive predictive value would then reflect the proportion of those who truly benefited from being given priority, i.e. the positive yield or effectiveness of the tool, which is important for cost effectiveness.

The final relationships could be defined as

$$\textbf{Effectiveness} \quad \alpha \quad \frac{\text{Accuracy of prioritisation tool x Prevalence}}{\text{Created Demand by the tool (which is dependent on specificity and sensitivity)}}$$

In summary effectiveness of a priority tool is directly proportional to the accuracy of prioritisation tool and inversely proportional to the created demand. Effectiveness is also higher when the relevant problem is common, i.e. the yield of a test would be high in spite of a lower accuracy

of a test. In contrast, in the situation where the prevalence of the health problem in question is low, an efficient tool in using allocated resources is reliant on a very accurate tool. For instance in breast cancer, a mammogram has a 41% sensitivity, 98% specificity to detect breast cancer in all women. As the incidence of breast cancer decreases with decreasing age the positive predictive value also decreases (i.e. the number of patients with cancer who had a positive mammogram) from 14% to 8% in those younger than 50 years. [83]

Chapter 3

Hypothesis and study design

Aims, hypotheses and study designs.

This thesis will investigate the benefit and possible use of diagnostic and symptomatic indices in streamlining those presenting with anaemia (primarily suspected to be iron deficient) in an attempt to predict site of cause of anaemia with reasonable accuracy.

Hypotheses

1. GI cancers present with different patterns of anaemia;
2. Blood indices can be used to differentiate cause of possible site of anaemia;
3. Symptom combinations can help in prediction of site of GI pathology;

As result of these hypotheses the ultimate hypothesis of this doctoral thesis is:

In patients presenting to secondary care with IDA for investigation, the combination of full blood count indices and symptom profiles can be used in a risk tool modelled to predict the likely site of cause of IDA.

Study design

To test the hypotheses several studies were conducted

1. Identifying independent factors that can be used in developing a prediction tool;

a. Study of haematological profiles of common GI malignancies (Chapter 4);
b. Prospective study of a cohort of patients referred with IDA, analysing their presenting symptoms and blood indices profile and their relationship with diagnosis and site of cause IDA (Chapter 5).

2. Design of a streamlining tool to predict likely site of cause of anaemia to aid in prioritising method of investigation. Comparing the prediction model and available current practice guidelines (Chapter 6).
    a. Primary outcome
        i. Accuracy of prediction of site of pathology
    b. Secondary Outcome
        i. Performance of tool against current guidelines
        ii. Stage of colon cancer as compared to pre and post protocol.

Chapter 4

Profile of anaemia in common GI malignancies

Profile of anaemia in common GI malignancies

Abstract

Iron deficiency anaemia (IDA) accounts for 3-14% of referrals to gastroenterology clinic. This is due to the high risk of GI cancer as a cause for chronic blood loss. Published guidelines for the investigation of anaemia aim to reduce the delay of diagnosis of patients with GI cancer. However, these guidelines differ in the definition and threshold of anaemia to trigger a referral. Furthermore, there is difference in presentation patterns of anaemia in colon cancer, with proximal colon cancer (PCC) presenting with IDA.

We aim to study the difference in pattern of anaemia between proximal colon cancer and common upper GI cancers and sensitivity of different guideline thresholds of referrals.

Over a three year period, between 1999 and 2001, patients referred with proximal colonic cancers, gastric and oesophageal cancers were studied and haematological profiles recorded.

Statistical analyses was performed using, t test, Mann-Whitney U test, ANOVA and Chi square test where appropriate.

159 (61 PCC, 43 gastric, 55 oesophageal) cancers were diagnosed during this period. Anaemia was significantly more prevalent in colon and

gastric cancers (75% & 67% respectively) as compared to oesophageal cancers (27%, p<0.0001).

Among anaemic patients colonic cancers had a significantly lower mean MCV and MCH (74[SD10] & 23[SD4] respectively) as compared to upper GI cancers. (Gastric 81[SD9] & 26[SD4], Oesophageal 80[SD9] & 26[SD4]). ($p < 0.01$). A higher proportion of PCC fulfilled the referral guidelines as compared to upper GI cancers. As the referral criteria became more specific the sensitivity to cancer detection decreased across all three cancer groups.

Different haematological profiles of GI cancers have been demonstrated. Using these profiles we could predict likely site of cancer. In order to detect a higher proportion of cancers the thresholds of referral need to be lowered.

Introduction

Anaemia and IDA in particular, is common in general practice especially in the aging population. It is estimated that 2 -5 % of adult men and postmenopausal women have IDA[1]. IDA is used as high risk criteria for urgent referral to secondary care. However it is not known what proportion of these patients attend secondary care for investigation.

It is estimated that 4-13% of referrals to a gastroenterology clinic are due to IDA [1]. Chronic blood loss from the GI tract commonly presents with

iron deficiency anaemia (IDA)[1, 38, 84]. Causes of such blood loss are vast, however GI malignancy remains the most significant [38-40, 42, 85, 86]. To avoid delay in diagnosis of asymptomatic colon cancer and upper GI cancer[5, 7, 10] the BSG [1],the DoH and NICE set guidelines in an attempt to optimise the investigation of patients who present with IDA and highlight those patients at high risk that required urgent referral. Recent audits of these guidelines however have not demonstrated any improvement in early cancer detection or stage of cancer. There is also a high proportion of GI cancer coming through routine referral pathways[19, 21, 87]. These problems were attributed to poor sensitivity and specificity of IDA to cancer, poor guideline compliance and thresholds set too low for referral (i.e. referral if HB < 10g/dl and 11 g/dl for women and men respectively). In addition there are conflicting reports on the association of cancer stage and anaemia with a tendency for anaemia being a late sign of cancer thus questioning the survival benefits of using anaemia as the diagnostic tool for detection and improving GI cancer survival[88].

Prior studies have reported that colon cancers have variable presentation profiles (e.g. PCC more commonly presents with IDA as compared to distal colon cancer(DCC)) and that the use of red blood indices can help in identifying the site of colonic cancer [11, 89, 90], but to date no

studies have specifically assessed the pattern profiles of upper GI cancers, and colon cancers with anaemia.

The aim of this study is to identify the differences in full blood count indices in the three common GI cancers and whether it is possible to differentiate between the proximal colon, gastric and oesophageal cancers based on blood indices profile.

Methods.

Hospital records were retrieved for consecutive patients diagnosed with PCC (caecal, ascending and transverse colon cancer), gastric cancer, and oesophageal cancer over a three year period from 1999 to 2001. A total of 61 patients with proximal colon cancers (PCC), 55 oesophageal, and 43 gastric cancers were identified and studied.

Haematological profiles from the FBC were assessed at the time of referral, diagnosis or up to 6 months prior to diagnosis in cases when iron or blood transfusions had been administered. Haemoglobin (Hb), Haematocrit (Hct), Red Blood Cell count (RBC), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC) and Red Distribution Width (RDW) were recorded.

Anaemia was accepted as < 11.5g/dl in women and < 13g/dl in men. The incidence of anaemia and patterns of blood indices were recorded and assessed for each GI cancer group.

Cancer detection rate comparisons were then conducted using the laboratory normal range, DoH guidelines, and BSG guidelines (Table 4.1). Statistical analysis was conducted using the t-test, Mann-Whitney U test, ANOVA and Chi-square test as appropriate. NCSS software (Kaysville, Utah, USA) was used to perform the analysis. P value of <0.05 was accepted as statistically significant.

Table 4.1: Criteria used for classification of anaemia for referral

Criteria for classifying anaemia	Definition
i. Anaemia as per laboratory normal value	Hb <13 g/dl in males, Hb<11.5 g/dl in females
ii. Microcytosis as per laboratory normal	MCV< 82 fl in males, MCV < 78 fl in females
iii. Local definition of IDA	Anaemia and Microcytosis as per laboratory limits(Hb <13 g/dl and MCV< 82 in males, Hb<11.5 g/dl and MCV< 78 in females
iv. Anaemia as per DoH referral criteria	Hb <11 g/dl in males, Hb <10 g/dl in females
v. DoH Criteria for Iron Deficiency Anaemia	Anaemia as defined by DoH criteria and MCV<76 fl
vi. BSG criteria for IDA	Hb less than normal for laboratory and MCV <76 fl or Ferritin < 15 ng/ml

Results

A total of 61 proximal colon (PCC), 55 oesophageal, and 43 gastric cancers were identified. There were no significant differences in the distribution of age and gender. (Table 4.2)

Table 4.2: Patient Demographics and full blood count profiles for cancer types

	PCC	Gastric Cancer	Oesophageal Ca	Total	*P*
Count	61	43	55	159	
Male(%)	30 (49%)	29 (67%)	33 (60%)	92 (58%)	
Female(%)	31 (51%)	14 (33%)	22 (40%)	67 (42%)	
Age(SD)	74.2 (11)	72.2 (11)	74.2 (10)	73.6 (11)	***0.6***
Hb(SD)	10.1(3)	10.8 (3)	12.8 (3)	11.2 (3)	***<0.01***
Count anaemic (%)	46 (75%)	29 (67%)	15 (27%)	90 (57%)	***<0.01***
RBC(SD)	4.2 (0.6)	4 (0.7)	4.5 (0.7)	4.2 (0.7)	***<0.01***
MCV(SD)	77.6 (10)	82.4 (8)	85.6 (7)	81.7 (9)	***<0.01***
MCH(SD)	24.2 (5)	26.6 (4)	28.6 (3)	26.4 (5)	***<0.01***
MCHC(SD)	311.6 (25)	319.7 (28)	332.1 (22)	320.9 (26)	***<0.01***
HCT(SD)	32 (6)	32.8 (6)	38.7 (7)	34.5 (7)	***<0.01***
RDW(SD)	16.2 (3)	15.1(2)	14.3 (2)	15.3 (2)	***<0.01***

The mean Hb was significantly lower in PCC and gastric cancer as compared to oesophageal cancer (Table 4.2). The pattern of all blood indices was significantly different between all cancer groups. PCC had a tendency to present with low MCV, MCH, MCHC, (ie microcytosis and hypochromia that is classically seen in iron deficiency anaemia) and a high RDW. Both gastric and oesophageal cancer overall had a normal MCV, MCH, and MCHC. (Table 4.3)

Table 4.3 Sub analyses of the anaemic cancer patients.

Anaemic Cancers		PCC	Gastric Cancer	Oesophageal Cancer	Total	*P*
Count		46	29	15	90	
Mean values	Age(SD)	75.3(10)	73.3(10)	80.1(9)	75.5(10)	
	Hb(SD)	9.1(2)	9.4(2)	9.4(2)	9.2(2)	***0.7***
	RBC(SD)	4(0.6)	3.7(0.5)	3.8(0.6)	3.9(0.6)	***0.04***
	MCV(SD)	74.4(10)	81.4(9)	80.1(9)	77.6(10)	***<0.01***
	MCH(SD)	22.5(4)	25.6(4)	25.1(4)	23.9(4)	***<0.01***
	MCHC(SD)	302.9(23)	310.4(29)	311.1(28)	306.7(26)	***0.3***
	HCT(SD)	29.5(5)	29.7(4)	30.7(5)	29.8(5)	***0.7***
	RDW(SD)	16.9(3)	15.7(2)	15.7(2)	16.3(3)	***0.1***

Anaemia is a significantly common feature of both gastric and proximal colon cancer as compared to oesophageal cancer. Although a higher proportion of PCCs present with anaemia as compared to gastric cancers, this difference did not reach statistical significance (p=0.8).

When the anaemia threshold was adjusted to the current DoH guideline recommendations (Table 4.4), the proportions of cancers detected reduced. This was compounded by using the addition of microcytosis (low MCV) resulting in a further reduction of sensitivity for each cancer group.

Table 4.4: Percentage of cancers fulfilling guideline's referral threshold criteria.

Criteria for anaemia (Criteria number in table 4.1)	PCC	Gastric Cancer	Oesophageal Cancer	Total
Count	**61**	**43**	**55**	**159**
Lab anaemia (i)	75%	67%	27%	57%
DoH anaemia (iv)	56%	51%	16%	41%
Lab Microcytosis (ii)	54%	40%	18%	38%
BSG Microcytosis (vi)	44%	21%	7%	25%
IDA (iii)	52%	33%	13%	33%
BSG IDA (vi)	44%	19%	7%	25%
DoH IDA (v)	39%	16%	7%	22%

However, among the different definitions for IDA, the local thresholds of anaemia and microcytosis (Hb and MCV less than the laboratory normal) had the highest sensitivity for each cancer group.

Discussion

This study highlights the significant difference in the blood indices profile of the common GI malignancies.

Investigations of both the upper and lower GI tract in patients with IDA have commonly yielded a higher incidence of upper GI causes [37, 64, 91]. However, colon cancer remains the most common cancer identified in these patients.

Studies of the value of blood indices in predicting colon cancer yielded a potential for differentiating PCC from distal colonic cancer [89, 90]. This study demonstrates a potential of differentiating upper and lower GI cancer using the full blood count indices. The higher incidence of anaemia, the low MCV and abnormal RDW in proximal colon cancer as compared to upper GI cancers confirm that proximal colon cancer results in iron deficiency pattern more commonly than upper GI cancer.

Spell et al [89] demonstrated that a higher RDW is sensitive to PCC even in the absence of anaemia. IDA in PCC could be explained by the fact that blood loss from proximal colon cancer is often occult and as it passes

through the colon there is no potential re-absorption of digested iron or heme. In contrast upper GI pathologies have the potential for a significant degree of re absorption of heme iron, the most bioavailable form of iron [92]. In upper GI cancer presenting in more brisk bleed (melaena), the blood index profile would be of acute haemorrhage hence the MCV and RDW remains normal.

Ferguson et al [93] demonstrated in a study using whole gut lavage as investigation of chronic blood loss that colonic cancer was the main pathology that resulted in a significant detectable blood loss as compared to subjects with a confirmed upper GI pathology expected to cause iron deficiency anaemia. This questions the causal relationship of IDA and upper GI pathology and raises the possibility of other mechanisms of cause of IDA in these subjects. Potential causes of IDA in upper GI cancer could be as a result of chronic malnutrition, co-existence of systemic disease, paraneoplastic phenomenon in addition to the presumed longstanding blood loss.

In the presence of normal oral intake and absorption of iron the balance between blood loss and iron intake determines the onset and severity of anaemia in PCC. Hence before anaemia develops, there is a stage of iron deficient haematopoiesis. In this situation the population of cells produced would be heterogeneous resulting in the raised RDW before

anaemia develops. Once the iron stores are depleted (low ferritin), the bone marrow continues to produce RBCs in the absence of adequate haemoglobin synthesis resulting in a drop in the haemoglobin contents of RBC (low MCH), and low hematocrit with a normal RBC count (low MCV). Ultimately this will slow erythrogenesis causing a drop of RBC count.

The use of different criteria as thresholds for high risk referral (Table 4.4) has demonstrated a difference in sensitivity for cancer detection. The pathogenesis of anaemia caused by GI cancer as described above explains the reduction of sensitivity to cancers when the thresholds of referrals are changed. Although there is no evidence to support the potential improved survival from detecting cancer referred with IDA early [89, 90], it is logical to use lower thresholds as criteria for referral so that the proportion of cancer detected is increased thereby increasing the potential of detecting early disease.

In summary, GI cancers have different anaemic profiles that have a potential to be used in streamlining investigation. The threshold of current guidelines needs to be adjusted to increase the yield of cancer detected in patients who develop anaemia.

Chapter 5

Prospective study of symptoms, blood profile and diagnosis of patients referred with anaemia for investigation

Prospective study of symptoms, blood profile and diagnosis of patients referred with anaemia for investigation

Abstract

Unexplained iron deficiency anaemia in men over the age of 40 and postmenopausal women is usually related to gastrointestinal chronic blood loss. Often these pathologies have associated symptoms, that if present, aid in the direction of investigation. Different blood indices patterns secondary to blood loss from the GI tract and systemic causes have been recognised (Chapter 4) . The aim of this study was to investigate the distribution of presenting symptoms and blood indices profiles in patients investigated for unexplained iron deficiency anaemia. Over a two year period, patients referred to a dedicated anaemia clinic with iron deficiency anaemia were included for data collection. Symptom profiles and blood indices were collected. All patients had the GI tract investigated by means of upper and lower GI endoscopy with or without barium enema. All patients were followed up for a minimum of 1 year. 125 patients were included in the final analysis. The mean age was 72.3 years old (SD 11.4), with 51% of the cohort being males. 34% were referred urgently by the GP. Upper GI endoscopy was completed in 94%

of the patients and lower GI evaluation by means of barium enema, colonoscopy or flexible sigmoidoscopy or combination of any was completed in 92%. There was poor compliance with faecal occult blood (FOB) testing. A final diagnosis was established in 95% of the patients with only 6 patients having completely normal GI tract investigations and no other cause of anaemia identified. In these 6 patients the anaemia resolved with iron replacement therapy (nutritional cause). Upper GI causes were the commonest cause of anaemia (40%) followed by systemic (30%) and then colonic (14%). Diverticular disease and gastritis were the commonest abnormalities identified. 21 patients (16%) had GI cancers with colonic cancer being the commonest (17 patients). 16% of the cohort had pathology at two sites or more. Dyspepsia and heart burn were the commonest upper GI symptoms. Dysphagia was rare but had the highest PPV for upper GI causes. Other symptoms did not have a high PPV for pathology or cancer. The mean Hb was 106 g/l (SD 15.2). Patients with cancer had lower Hb, MCV, and HCT. Patients with lower GI pathology had a trend towards a lower Hb, MCV, and MCH.
Individual symptoms did not aid in predicting a site of blood loss. In contrast, blood indices helped in predicting site of blood loss. There was a poor compliance with referral guidelines.

Introduction

DoH criteria for urgent referral for suspected upper and lower GI cancer use anaemia with or without a group of GI symptoms as high risk for cancer. Lower GI symptoms have a better cancer predictive value as compared to upper GI symptoms [16, 74, 80]. However, both symptom groups have poor specificity (as discussed in previous chapter).

GI tract investigations carry a relative risk of morbidity in view of the invasive nature of the tests. Hence it would be prudent to increase the specificity of any tool to reduce the unnecessary GI tract instrumentation.

A prioritisation tool that uses the combination of predictive power of both symptoms and blood profile to identify the probability of cause of anaemia would help streamline patients to the appropriate test thereby decreasing the risk of unnecessary investigation. In order to develop such a tool, the diagnostic value of presenting symptoms in this population and blood profile needs to be established.

We aim in this chapter to identify the diagnostic value of GI symptoms and blood profiles in predicting the site of GI pathology of patients referred for investigation of unexplained anaemia.

Study design and methods

Over a 2 year period from October 2003 to October 2005 patients referred to the hospital for investigation of IDA were included into the study. All patients were interviewed in a dedicated anaemia clinic.

The anaemia clinic was conducted by the main author (M Ballal), assisted by a nurse practitioner. Two other clinicians (D Smith, H Ballal) provided cover when the author was unavailable. They received appropriate training to ensure consistency and adherence to clinic protocol. The clinic was conducted once a week.

When a patient was referred by their general practitioner (GP) to general surgery clinic or to one of the gastroenterology consultant's clinic (Dr J MacKay) for investigation of unexplained IDA, the referral was directed to the dedicated anaemia clinic. The usual practice was for the GP to classify the referral as urgent (i.e. to be seen within two weeks), soon (within 6 weeks), or routine. Patients' symptoms and physical examination findings were recorded using a structured history and examination proforma (Appendix 2). The proforma was used to standardise the information gathered and aided in ensuring all patients' relevant tests and investigations were booked into the hospital system. Patients had a FBC, iron studies, Folic acid and B12 measured. They were also requested to provide a 3 separate stool samples for guaiac-based FOB test and urine collected for urinalysis.

Patients who were younger than 45 years, or who had been commenced on iron prior to blood analysis, or those who were unfit for investigation, or those who did not give consent for investigation, or who did not complete their GI investigations were excluded from the study.

All patients had an upper GI investigation in the form of an OGD (oesophago-gastro-duodenoscopy) with biopsies where indicated, and lower GI investigation in the form of an endoscopic examination (flexible sigmoidoscopy or colonoscopy), barium enema or both in cases where one was incomplete (caecum not fully assessed). The order of the investigations was decided by the reviewing clinician based on clinical judgement at the time of testing and availability of investigation slots.

Any biopsies taken were performed by the endoscopist based on findings at the time. Duodenal biopsy was requested as a routine, however it was not performed routinely due to variation in endoscopist preference.

If no cause for the IDA was identified in the GI tract then an assessment by haematologist was carried out. When a diagnosis was not established a FBC was repeated and if anaemia resolved no further intervention was carried out. However, if anaemia was persistent then a lower GI assessment is repeated with an alternative modality.

Patients where followed up for a minimum of 1 year.

Statistical analysis was conducted using NCSS (2004) software (Kaysville, Utah, USA). The t- test, Mann-Whitney U test, Chi –Square test, Fisher Exact test were used for test of significance where appropriate. P value of <0.05 was used as significant. Due to the large number of independent variables interrogated in this study a Bonferroni correction for multiple testing was considered. The corrected level of significance based on this is a P value of < 0.00012.

Sample Size

This is a prospective pilot study that aims to develop a tool to investigate patients presenting with IDA. The results will form the foundation of a larger trial to validate the developed tool.

An accurate representative sample of the population of IDA patients referred to secondary care is required. Based on literature review it is expected that 70 % (95% CI 60-80) of the investigated anaemic population will have a GI cause of anaemia (Chapter 1, table 1.8). To obtain a representative sample of the investigated population with a type one error probability of 5% a minimum of 81 anaemic patients is needed.

Based on previous reports the cancer detection rate varies from 5% to 37%. To achieve a cancer detection rate of 14 % (95%CI 8-20%) (Chapter

1, table 1.8) then it would require 100 anaemic patients to be investigated with a maximum of type one error probability of 5%. Hence a minimum of 100 patients is required to have a representative sample of the IDA population referred to secondary care.

Results

A total of 147 patients were referred during the study period for investigation. 22 were excluded from the study, 4 were not anaemic (that is referred in error), 8 were unfit for assessment, 3 had been commenced on iron at the time of referral, 5 were younger than 45 years and 2 did not give consent.

Thus 125 patients were eligible for inclusion into the analysis. Three patients whose anaemia had resolved prior to referral but had remained either microcytic or iron deficient at time of investigation and were included.

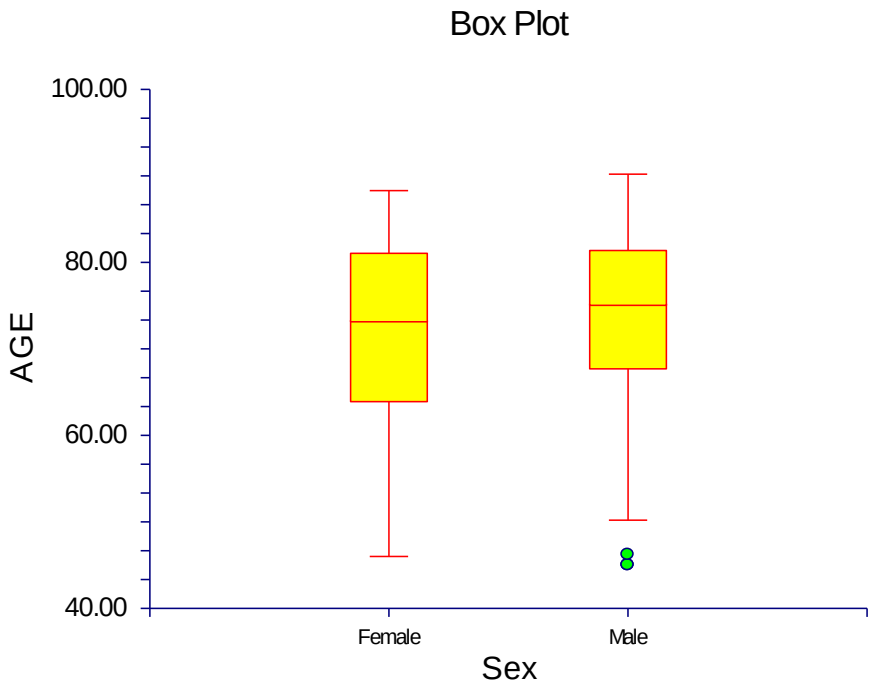
Demographics

The average age of patients studied was 72.3 (SD 11.4) ranging from 45 to 90 years old and a median of 74.4.

Gender distribution was equal (*p=0.9*) with 51% (95% CI 40-58%) male patients. The age distribution was equal between gender groups (*p=0.5)*

with the age of females averaging 71.6(SD11.4) and males 72.9(SD11.6) (figure 5.1).

Figure 5.1: Box plot for age distribution and gender.



Urgent referrals as stated by the GP accounted for 34% of the total and the remainder 66% of our subjects were referred routinely.

Investigation modalities

Upper GI Endoscopy:

Upper GI endoscopy was performed on 117 (94 %) of the referred patients. Of the remainder, 5 (5%) had a colon cancer identified prior to date of endoscopy and the patients did not wish to proceed with an OGD and 2 (1%) had overt other causes (1 bladder cancer and renal failure, 1 hypothyroidism).

A Helicobacter pylori urease test via a gastric biopsy was completed 73% of the time with a 26% positive rate. Gastric and low duodenal biopsies were performed in 25% with a 51.7% positive rate for gastric or duodenal pathology. Coeliac disease screening was only performed in suspected patients as the hospital did not fund the test routinely.

Lower GI Investigations:

Table 5.1 demonstrates the combinations of diagnostic modalities of lower GI tract. The entire lower GI tract was visualised in 92% of the patients; 8 had flexible sigmoidoscopy only and 3 underwent a CT scan and no intra-luminal assessment.

Table 5.1: Mode of investigation of lower gastrointestinal tract

Modality of assessment of Lower Gastrointestinal tract	Count(%)	Mean Age
Flexible Sigmoidoscopy and Barium enema	63(51%)	72
Colonoscopy	19(15%)	72
Barium enema	14(11%)	74
Flexible sigmoidoscopy, Colonoscopy and Barium enema	8(6.5%)	67
Flexible sigmoidoscopy	8(6.5%)	77
Colonoscopy and Barium enema	6(5%)	74
Flexible sigmoidoscopy and Colonoscopy	4(3%)	74
CT scan	3(2%)	75

A combination of flexible sigmoidoscopy and barium enema was the commonest modality of investigation of the lower GI tract followed by colonoscopy alone. The population investigated was elderly and hence colonoscopy was chosen only for those patients who were considered medically fit enough to have such an invasive procedure. If a pathology

was encountered on flexible sigmoidoscopy that required evaluation of the reminder of the colon a colonoscopy was performed if assessment revealed the patient to be medically fit. Lower GI tract was evaluated by means of a CT scan in 2% of the patients who could not tolerate bowel preparation.

Faecal Occult Blood test (FOB):

Compliance with FOB testing was poor. FOB was returned by 25% (31) of the patients. FOB was positive in 6% of the total cohort and 25% of the submitted FOBs (Table 5.2).

In patients who submitted FOB samples, 29% of patients who had upper GI pathology tested positive for occult blood, 43% of patients with lower GI pathology tested positive for occult blood. None of the patients with non-GI pathologies had a positive FOB test. Of all patients with GI cancers only one patient who had PCC submitted a sample for FOB testing and tested positive for all three samples.

Table 5.2: Faecal occult blood and site of cause of anaemia.

FOB	Total	Upper GI pathology	Lower GI pathology	Non GI causes of anaemia	Upper GI cancer	Lower GI Cancer
Positive	8	6	3	0	0	1
Negative	23	15	4	6	0	0
Not done	94	43	24	35	4	13
Total	125	64	31	41	4	14

Diagnosis

A cause of anaemia was established in 119 (95%) of the patients, table (5.3). 6 patients had a completely normal gastrointestinal tract and a low serum iron with anaemia resolving following iron administration. At the 1 year follow up of these patients no additional GI tract pathology had been diagnosed. Anaemia was attributed to iron nutritional deficiency.

Table 5.3: Final diagnosis in all patients investigated.

Final Diagnosis	No. of patients
Alcoholic Liver Disease(ALD)and Duodenitis	1
ALD and Hiatus hernia (HH)	1
ALD+ *Helicobacter Pylori (HP)* Gastritis+ Oesophagitis+ Distal Colonic Polyps	1
Anaemia of chronic disease	1
Anaemia of chronic disease and HH and Severe Diverticular disease(DD)	1
Auto-immune PGAD	1
Barrett's Oesophagus and Mild DD	3
Barrett's Oesophagus, Chronic Gastritis, Thalassemia	1
Barrett's Oesophagus, duodenitis and Mild DD	1
Cholangiocarcinoma, *HP* gastritis	1
Chronic Renal Failure (CRF)	2
Chronic Renal Failure and D polyp	1
Chronic Renal Failure and Duodenitis	1
Chronic Renal Failure and HH	1
Chronic Renal Failure and Mild DD	1
Distal Colonic Cancer	4
Distal Colonic polyp	1
Duodenitis and HH mild DD	1

Duodenitis, *H Pylori* mild DD	1
Gastric Cancer	3
Gastric Dysplasia and Distal Colonic Polyp	1
Gastric polyp AND mild DD	1
Gastric polyps	1
Gastric Ulcer	1
Gastric Ulcer and Mild DD	1
Gastritis	3
Gastritis , Mild DD	5
Gastritis and Colitis	1
Gastritis and Distal Colonic Polyps	1
Gastritis and HH and Mild DD	1
Gastritis and Mild DD	1
Gastritis and Oesophageal Varices	1
Gastritis, mild DD and Distal Colonic Polyp	1
H Pylori and HH	1
H Pylori and Oesophagitis and Mild DD	1
H Pylori Gastritis and Mild DD	1
*H Pylori G*astritis, diverticular, sigmoid polyp	1
H Pylori Gastritis	6
Hiatus Hernia and gastritis	1
Hiatus Hernia and Vascular malformation	1
Hiatus Hernia	3
Hiatus Hernia and mild DD	2
Hypothyroidism	1
Inflammatory Bowel Disease	1
Lung Cancer and Mild DD	2
Myelodysplastic syndrome(MDS) and Distal Colonic Polyp	1
MDS and Hiatus Hernia	1
MDS and Severe DD	1
MDS, *H Pylori* Gastritis and Mild DD	1
Menorrhalgia and HH	1
Mild DD and Oesophageal ulcer	1
Mild DD, Distal Colonic Polyp and HH	1
Mild to Moderate Diverticular Disease(DD)	10
Moderate DD and HH	2
Myelodysplastic Syndrome(MDS)	3
Normal GI tract and no cause identified.	6
Oesophageal Stricture	1
Oesophagitis	2
Oesophagitis, Vascular telangiectasia	1
On Warfarin for heart valve replacement and Mild Diverticular disease	1
PCC, Barrett's, Duodenal Polyp	1
Postop Bleed and Severe DD	1
Postop bleeding from Total knee Replacement	1
Proximal Colonic Cancer	6
Proximal Colonic Cancer and Mild DD	1
Proximal Colonic Cancer and Gastric Ulcer	1
Proximal Colonic Cancer and Gastritis	1
Proximal Colonic Cancer, Gastritis AND Mild DD	1
Proximal Colonic Cancer and *H Pylori* Gastritis and Mild DD	1
Proximal Colonic Cancer and HP Gastritis	1
Proximal Colonic Polyp	1

Proximal Colonic Polyp and Gastric Polyp	1
Proximal Colonic Polyp and Gastritis	1
Rheumatoid Arthritis and Mild DD	2
Severe DD and Duodenal polyp	1
Severe DD and HH and Barrett's Oesophagus	1
Severe Diverticular Disease	3
Total	125

Diverticular disease and gastritis were the commonest pathologies identified in the cohort, Table (5.4).

Table 5.4: Diagnosis groups in patients investigated for anaemia.

Site	Final Diagnosis	No. of Patients	%
Lower GI	Mild to moderate Diverticular Disease	44	35%
Upper GI	Gastritis	20	16%
Upper GI	Hiatus Hernia	19	15%
Upper GI	*Helicobacter Pylori* Gastritis	16	13%
Systemic	Systemic conditions(CRF, RA, Hypothyroid, recent postop bleed)	13	10%
Lower GI	Proximal Colonic Cancer	13	10%
Lower GI	Distal colonic polyp	9	7%
Systemic	Haematological Conditions	9	7%
Lower GI	Severe Diverticular Disease	8	6%
Upper GI	Barrett's Oesophagus	7	6%
Upper GI	Oesophagitis	7	6%
Upper GI	Duodenitis	5	4%
Lower GI	Distal Colonic Cancer	4	3%
Systemic	Alcoholic Liver Disease	3	2%
Upper GI	Gastric Cancer	3	2%
Upper GI	Gastric Polyp	3	2%
Upper GI	Gastric Ulcer	3	2%
Lower GI	Proximal Colonic Polyp	3	2%
Upper GI	Duodenal Polyp	2	2%
Lower GI	Inflammatory Bowel Disease	2	2%
Systemic	Lung Cancer	2	2%
Upper GI	Gastric Vascular Malformations	2	2%
Upper GI	Cholangiocarcinoma	1	1%
Upper GI	Gastric Dysplasia	1	1%
Systemic	Gynaecological Bleeding	1	1%
Upper GI	Oesophageal Varices	1	1%
Systemic	Normal GI (Nutritional iron deficiency)	6	5%

As discussed in chapter 1 mild to moderate diverticular disease and uncomplicated hiatus hernia are not recognised as causes of chronic occult blood loss from the GI tract [63, 77, 94-96]. Mild diverticular

disease and/or uncomplicated hiatus hernia was the only pathology identified in 15 patients.

GI cancer was identified in 21 (16%) patients (13 proximal, 4 distal colonic cancer, 3 gastric cancers and 1 cholangiocarcinoma.) Non GI cancers were identified in 2 (2 lung cancers). One patient who was known to have bladder cancer that developed renal failure, and had new onset anaemia and hence was referred to the clinic to rule out GI cause of anaemia.

Distribution of significant cause of anaemia based on site is listed in table 5.5. Significant causes were defined as pathology that results in blood loss or decreased haemoglobin synthesis. Mild to moderate diverticular disease and non-complicated hiatus hernia were therefore excluded from causes of blood loss in the GI tract. For those with no GI cause of anaemia a site of systemic cause was recorded.

Table5.5: Distribution of significant causes of anaemia.

Site of main cause of anaemia	No of Patients	% of the total	Patients with cancer	Site specific cancer incidence
Upper GI disease	50	40%	4	8%
Systemic causes	38	30%	2	5%
Colonic disease	17	14%	11	65%
Upper GI and colonic disease	11	9%	6	55%
Upper GI and systemic disease	6	5%		
Colonic and systemic disease	2	2%	2	100%
Upper GI, colonic and systemic disease	1	1%		

The upper GI tract was the commonest source of chronic blood loss (40%). However, the lower GI tract had the highest incidence of cancer as cause of chronic blood loss with 17 malignancies (13 proximal and 4 distal colon cancers). In 16% of the patients more than one site was the cause of anaemia. It is important to note that colon cancer was identified in 55% of the patients with dual upper and lower GI pathology. In 30.4 % of the cohort no GI source of blood loss could be identified.

Symptoms profile

Following a structured interview using the symptoms proforma (Appendix 2), all patients' symptoms were recorded and physical examination findings recorded.

All 125 patients eligible for the study were analysed.

Positive predictive values (PPV) of symptoms and past medical history for site of main cause of anaemia and cancer is summarised in tables 5.6 and 5.7.

Heart burn and dyspepsia were the highest reported upper GI symptoms. In the presence of these symptoms, an upper GI cause of anaemia was found (PPV) in 69% and 66% respectively. However, when un-complicated hiatus hernia was removed, the PPV of heart burn and dyspepsia decreased to 48 and 50% respectively. It would have been expected in the presence of dyspepsia and anaemia that these patients

should have been referred urgently. In contrast to these expectations only 28% of dyspeptic patients with anaemia were referred urgently. Interestingly, the PPV of these two upper GI symptoms to distal colonic causes of anaemia was similar to significant upper GI causes (50%, 44% respectively). The PPV of these symptoms for cancer was low (13%, 22%) confirming the lack of sensitivity and specificity of these symptoms for malignancy. Dysphagia was only reported in 9 (7%) patients. Only 22% of these patients were referred urgently. The PPV of dysphagia for significant upper GI cause was 78%. As there was no patient with oesophageal cancer the PPV for Upper GI cancer was 0.

None of the upper GI symptoms had a significant difference in their distribution with respect to cause of anaemia, type of cancer or route of referral (chi-square and fisher exact test where appropriate.)

Change in bowel habit to loose motion or alternating loose motion and constipation was the commonest lower GI symptom reported. Upper GI causes of anaemia were more common in patients reporting change in bowel habit than patients with significant distal colonic pathology. In contrast increased frequency of bowel motion, although not common, was associated with a higher predictive value to distal colonic cause (PPV 57%). Proximal colonic causes as expected had relatively low symptom prediction. None of the lower GI symptoms had a significant prediction

power to site of cause of anaemia or cancer. Constipation was higher in patients with upper GI cancer (22%, *p=0.02* using Fisher exact test, however not significant when corrected for multiple tests using Bonferonni correction).

Weight loss was reported in 32 (25%) of patients. Only 28% of patients with weight loss and anaemia have been referred through urgent routes. In patients reporting weight loss , anaemia was attributed to an upper GI cause, a significant upper GI disease and distal colonic disease in 50%, 44% and 47% respectively. Only 13% of patients with weight loss had a proximal colonic cause of anaemia and none of the patients with weight loss had a significant distal colonic cause. With respect to all cancer, 19% of patients in this study reporting weight loss had cancer.

Loss of appetite was reported in 20% and had a similar distribution to weight loss, except for a tendency to be have a lower PPV to distal colonic causes of anaemia.

NSAID or aspirin use was reported in 53 (43%) patients. It was interesting to note that patients who were taking aspirin had a tendency to have a lower incidence of proximal colon diseases, cancer in general and lower GI cancer.

Table 5.6: Positive predictive values of presenting symptoms and past medical history with respect to type of referral and site of cause of anaemia.

Symptom and PMH	Total	Urgent referrals (%)	No cause identified (%)	Upper GI cause (%)	Significant upper GI cause (%)	Proximal colonic cause (%)	Distal colonic cause (%)	Significant distal colonic cause (%)	Systemic cause (%)
Pre menopausal Women	3	1 (33%)	0 (0%)	3 (100%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)
Heavy period	1	0 (0%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Upper GI symptoms									
Heart burn or reflux	48	19 (40%)	8 (17%)	33 (69%)	23 (48%)	4 (8%)	24 (50%)	6 (13%)	11 (23%)
Dyspepsia	32	9 (28%)	5 (16%)	21 (66%)	16 (50%)	4 (13%)	14 (44%)	5 (16%)	6 (19%)
Upper abdominal pain	14	5 (36%)	2 (14%)	9 (64%)	7 (50%)	1 (7%)	5 (36%)	0 (0%)	2 (14%)
Nausea	11	3 (27%)	3 (27%)	7 (64%)	4 (36%)	1 (9%)	4 (36%)	0 (0%)	1 (9%)
Vomiting	7	4 (57%)	2 (29%)	4 (57%)	2 (29%)	0 (0%)	4 (57%)	2 (29%)	0 (0%)
Dysphagia	9	2 (22%)	0 (0%)	8 (89%)	7 (78%)	1 (11%)	6 (67%)	1 (11%)	0 (0%)
Previous history of gastric surgery	3	2 (67%)	0 (0%)	3 (100%)	3 (100%)	0 (0%)	2 (67%)	0 (0%)	0 (0%)
Melena or Hematemesis	8	2 (25%)	1 (13%)	4 (50%)	4 (50%)	1 (13%)	5 (63%)	1 (13%)	2 (25%)
Lower GI symptoms									
Small bowel surgery	2	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Blood in stool	17	6 (35%)	0 (0%)	14 (82%)	12 (71%)	1 (6%)	9 (53%)	2 (12%)	4 (24%)
Change in bowel habits to loose motion	43	16 (37%)	7 (16%)	25 (58%)	19 (44%)	3 (7%)	24 (56%)	6 (14%)	6 (14%)
Slime in stool	8	3 (38%)	1 (13%)	5 (63%)	3 (38%)	0 (0%)	5 (63%)	3 (38%)	2 (25%)
Increased frequency of stool	7	3 (43%)	2 (29%)	2 (29%)	2 (29%)	1 (14%)	4 (57%)	2 (29%)	2 (29%)
Constipation	9	1 (11%)	2 (22%)	6 (67%)	6 (67%)	0 (0%)	2 (22%)	1 (11%)	2 (22%)
Central or lower abdominal pain	28	11 (39%)	5 (18%)	17 (61%)	14 (50%)	5 (18%)	13 (46%)	3 (11%)	5 (18%)
History of Inflammatory bowel disease	4	2 (50%)	1 (25%)	2 (50%)	0 (0%)	0 (0%)	2 (50%)	1 (25%)	1 (25%)
History of Polyps	3	1 (33%)	0 (0%)	2 (67%)	0 (0%)	1 (33%)	2 (67%)	1 (33%)	0 (0%)
Family history of colon cancer	7	3 (43%)	1 (14%)	5 (71%)	2 (29%)	1 (14%)	4 (57%)	2 (29%)	1 (14%)
Right iliac fossa (RIF) pain	8	3 (38%)	1 (13%)	4 (50%)	2 (25%)	0 (0%)	5 (63%)	1 (13%)	3 (38%)

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Continue table (5.6): Positive predictive value of presenting symptoms and past medical history with respect to type of referral and site of cause of anaemia

Symptom and PMH	Total	Urgent referrals (%)	No cause identified (%)	Upper GI cause (%)	Significant upper GI cause (%)	Proximal colonic cause (%)	Distal colonic cause (%)	Significant distal colonic cause (%)	Systemic cause (%)
Systemic Symptoms									
Weight loss	32	9 (28%)	6 (19%)	16 (50%)	14 (44%)	4 (13%)	15 (47%)	0 (0%)	7 (22%)
Loss of appetite	25	8 (32%)	2 (8%)	14 (56%)	11 (44%)	5 (20%)	8 (32%)	1 (4%)	3 (12%)
Brittle or abnormal nails	3	0 (0%)	0 (0%)	2 (67%)	2 (67%)	0 (0%)	2 (67%)	1 (33%)	0 (0%)
Sore tongue	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Night sweats	2	0 (0%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Pruritus	2	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Joint pain	14	4 (29%)	0 (0%)	10 (71%)	9 (64%)	0 (0%)	10 (71%)	1 (7%)	3 (21%)
Past Medical and Drug history									
PMH of RA	4	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)	1 (25%)	2 (50%)
PMH of Chronic renal failure	8	2 (25%)	2 (25%)	4 (50%)	3 (38%)	1 (13%)	2 (25%)	1 (13%)	5 (63%)
On NSAIDS or Aspirin	53	16 (30%)	7 (13%)	34 (64%)	28 (53%)	3 (6%)	31 (58%)	3 (6%)	11 (21%)
On Steroids	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
On Warfarin	9	1 (11%)	0 (0%)	6 (67%)	5 (56%)	3 (33%)	5 (56%)	1 (11%)	2 (22%)

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Table 5.7: Positive predictive value of presenting symptoms and past medical history with respect to cancer.

Symptom and PMH	Cancer	UG ca	LG ca	Non GI cancer
Pre menopausal Women	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Heavy period	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Upper GI symptoms				
Heart burn or reflux	6 (13%)	0 (0%)	5 (10%)	1 (2%)
Dyspepsia	7 (22%)	2 (6%)	5 (16%)	0 (0%)
Upper abdominal pain	2 (14%)	1 (7%)	1 (7%)	0 (0%)
Nausea	1 (9%)	0 (0%)	1 (9%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	1 (11%)	0 (0%)	1 (11%)	0 (0%)
Previous gastric surgery	1 (33%)	1 (33%)	0 (0%)	0 (0%)
Melena or Hematemesis	1 (13%)	0 (0%)	1 (13%)	0 (0%)
Lower GI symptoms				
small bowel surgery	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Blood in stool	3 (18%)	1 (6%)	2 (12%)	0 (0%)
Change in bowel habits to loose motions	7 (16%)	3 (7%)	4 (9%)	0 (0%)
Slime in stool	1 (13%)	0 (0%)	1 (13%)	0 (0%)
Increased frequency of stool	1 (14%)	0 (0%)	1 (14%)	0 (0%)
Constipation	3 (33%)	2 (22%)	0 (0%)	1 (11%)
Abdominal pain (Central or lower)	7 (25%)	0 (0%)	6 (21%)	1 (4%)
History of Inflammatory bowel disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)
History of Polyps	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Family history of colon cancer	1 (14%)	0 (0%)	1 (14%)	0 (0%)
Right Iliac Fossa (RIF) Pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Systemic Symptoms				
Weight loss	6 (19%)	2 (6%)	4 (13%)	0 (0%)
Loss of appetite	5 (20%)	0 (0%)	0 (0%)	0 (0%)
Brittle or abnormal nails	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sore tongue	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Night Sweats	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Joint pain	2 (14%)	2 (14%)	0 (0%)	0 (0%)
Past Medical and Drug history				
PMH of RA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PMH of Chronic Renal Failure	2 (25%)	0 (0%)	2 (25%)	0 (0%)
On NSAIDS or Aspirin	5 (9%)	1 (2%)	3 (6%)	1 (2%)
On Steroids	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On Warfarin	2 (22%)	0 (0%)	2 (22%)	0 (0%)

Blood indices profile

All 125 patients studied had their full blood count assessed. The mean haemoglobin (Hb) of the cohort studied was 106 g/l (SD 15.2g/l). The average Hb was significantly lower in females (p=0.001) as well as patients with cancer (p=0.0001) (significant level p value after Bonferroni correction is 0.002) (Table 5.8).

Females had a lower Hb, HCT, MCV MCH, MCHC and ferritin as compared to men. There was no difference in RBC, RDW, serum iron levels, vitamin B12 or Folate.

Patients with cancer had a significantly lower mean Hb, HCT, and MCV. There was no significant difference between those with cancer and those without with regard to the serum iron, ferritin, vitamin B12 and Folate (Table 5.8).

When the blood indices were compared with respect to the site of main cause of anaemia, there was a tendency for patients with lower GI disease as cause of anaemia to have lower Hb, low MCV and a low MCH. This tendency did not reach statistical significance (Table 5.9).

Table 5.8: Mean and standard deviation of blood indices with respect to gender and cancer

Sex	No of Patients	Mean of blood index(SD)										
		Hb	**RBC**	**HCT**	**MCV**	**MCH**	**MCHC**	**RDW**	**Iron**	**ferritin**	**B12**	**FA**
Total	**125**	106.1(15.2)	4.1(0.7)	33.8(4)	84(9.9)	26.4(4.2)	313.2(20.8)	16.3(2.6)	10.1(9.2)	71.7(84.4)	389.5(230)	9.2(8.2)
Male	**64**	110.3 (15.2)	4.1 (0.8)	34.6 (4.2)	86 (10.3)	27.2 (4.3)	317.3 (15.6)	15.9 (2.1)	11.5 (10.4)	83.8 (78.5)	356(214.8)	10 (10.6)
Female	**61**	101.6 (14)	4 (0.5)	32.8 (3.5)	82 (9.2)	25.4 (4.1)	309 (24.6)	16.6 (3)	8.7 (7.8)	60.6 (88.8)	417 (242.3)	8.3 (4.9)
p value		0.001	0.37	0.01	0.026	0.016	0.026	0.14	0.08*	0.02*	0.07*	0.7
Cancer	**23**	94.1 (17.5)	4 (0.5)	31 (4.4)	78.1 (9.9)	23.7 (4.5)	302 (21.5)	17.2 (2.6)	10.1 (12.4)	54.7 (77.3)	454 (272.8)	9.6 (5.8)
Non Cancer	**102**	108.8 (13.3)	4.1 (0.7)	34.4 (3.6)	85.4 (9.5)	26.9 (4)	315.8 (19.9)	16 (2.6)	10.1 (8.6)	74.8 (85.6)	378 (221.4)	9.1 (8.6)
p value		0.0001*	0.46*	0.0004*	0.001*	0.004*	0.004*	0.019*	0.4	0.15	0.4	0.7

T test was used to compare means. *Mann-Whitney U test was used if the data was not normally distributed.

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Table 5.9 : Mean and standard deviation of blood indices with respect to main site of cause of anaemia

Site of Cause of Anaemia	No of Patients	Mean of blood index(SD)										
		Hb	RBC	HCT	MCV	MCH	MCHC	RDW	Iron	Ferritin	B12	FA
Upper GI disease	50	106.9 (15.3)	4.2 (0.7)	34.1 (4.1)	83.1 (10.9)	26.2 (4.8)	313.1 (27.2)	16.4 (2.7)	9.7 (8.4)	56.5 (64.6)	397.5 (205.4)	9.3 (4.8)
Systemic causes	38	108.6 (13.3)	4 (0.6)	34.1 (3.8)	87 (8.5)	27.7 (3.3)	317.9 (12.7)	15.7 (2.1)	9.5 (6.2)	95.8 (98)	338.7 (219.8)	7.7 (6.1)
Colonic disease	17	98.6 (17.6)	4.1 (0.5)	32 (4.5)	78.9 (8.3)	24.3 (3.6)	306.7 (16.1)	17.2 (2.7)	7.2 (6)	28.4 (48.1)	303.9 (144.4)	15.2 (19.7)
Upper GI and colonic disease	11	101.4 (16.1)	4.1 (0.4)	33.1 (3.6)	81.5 (10.5)	25 (4.6)	304.7 (18)	17.2 (3.9)	17.6 (21.7)	92.1 (137.6)	640.9 (387.7)	7.4 (4.6)
Upper GI and systemic disease	6	116.8 (10.6)	4.4 (1.2)	35.3 (3.5)	89.3 (6.8)	27.3 (4.8)	325.4 (3.1)	14.9 (1.3)	13 (5)	100.8 (79)	341.5 (113.3)	8.2 (2.1)
Colonic and systemic disease	2	103.5 (6.4)	3.5 (0.2)	32.8 (2.1)	93.3 (1.3)	29.4 (0.4)	315 (0)	14.5 (1.7)	10.5 (2.1)	102.5 (16.3)	552 (172.5)	8.1 (1.5)
Upper GI, colonic and systemic disease	1	90	3.8	31.5	83.6	23.9	286	15.9	3	10	479	7.5

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Amongst those patients with cancer, the MCV and MCH were lower in patients with cancer in the GI tract compared with those with non GI tract cancers. This did not reach statistical significance (Table 5.10).

When the anaemia thresholds for referral guidelines were applied to the cohort it was apparent that highest sensitivity across all different criteria was for a colonic cause for anaemia (Table 5.11).

Discussion

In this section a cohort of patients referred by their GPs with unexplained anaemia underwent an upper and/or lower GI investigation. A cause was identified in 95% of patients. 6 patients had iron deficiency responding to iron and resolved completely with no further pathology identified at one year of follow up. High compliance with invasive investigations was observed, although compliance with FOB testing was poor (25%).

This study confirmed what was previously reported in literature[59, 60, 62, 63, 76, 97-106] that upper GI causes of occult blood loss are the commonest (40%), followed by systemic (30%) and lower GI causes (14%). Cancer incidence was highest in the lower GI tract with 65% of the patients with a lower GI cause of anaemia having colon cancer followed by patients who had

Table 5.10: Mean and standard deviation of blood indices with respect to type of cancer

Final Diagnosis	No OF patients	Mean of blood index(SD)										
		Hgb	RBC	HCT	MCV	MCH	MCHC	RDW	Iron	ferritin	B12	FA
Proximal colonic cancer	13	93.7 (16.3)	3.9 (0.5)	31 (4.2)	79.1 (10.8)	24 (4.6)	301.1 (16.7)	16.8 (2.7)	12.8 (15.8)	33.8 (55.5)	538.3 (300)	8.8 (4.8)
Distal colonic cancer	4	93 (17.5)	4.3 (0.4)	31 (4.7)	72.5 (7.9)	21.8 (3.5)	299.8 (17.5)	18.3 (1.6)	8.3 (7.8)	20.5 (20.5)	216.5 (62)	14.6 (13.3)
Gastric Cancer	3	93.7 (12)	4 (0.7)	30.8 (2.6)	77.8 (8.6)	24 (5.9)	305.3 (39.9)	18.1 (4.3)	5 (3)	95 (120.8)	445.3 (190)	9.9 (4.8)
Lung Cancer	2	115.5 (19.1)	4.1 (0.2)	35.4 (5.9)	86.6 (10.8)	28.3 (3.5)	327 (0)	16.2 (1.9)	7	190	190	5.4
Cholangiocarcinoma	1	62	3.3	23.5	71	18.7	264	17.7				

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Table 5.11: Distribution of different referral guidelines thresholds and main site of cause of anaemia.

Site of cause of anaemia	Total	Number of Patients meeting referral criteria(%)					
		Anaemia	Microcytosis	BSG	DoH	IDA	DoH IDA
Upper GI disease	50	47 (94%)	17 (34%)	20 (40%)	14 (28%)	22 (44%)	9 (18%)
Systemic causes	38	35 (92%)	11 (29%)	7 (18%)	14 (37%)	12 (32%)	2 (5%)
Colonic disease	17	17 (100%)	10 (59%)	9 (53%)	9 (53%)	11 (65%)	7 (41%)
Upper GI and colonic disease	11	11 (100%)	4 (36%)	5 (45%)	6 (55%)	6 (55%)	3 (27%)
Upper GI and systemic disease	6	6 (100%)	0 (0%)	1 (17%)	1 (17%)	1 (17%)	0 (0%)
Colonic and systemic disease	2	2 (100%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)
Upper GI, colonic and systemic disease	1	1 (100%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)
All cancers	23	23 (100%)	16 (70%)	19 (83%)	16 (70%)	19 (83%)	13 (57%)
Cancers of the Upper GI tract	4	4 (100%)	3 (75%)	3 (75%)	3 (75%)	3 (75%)	3 (75%)
Cancers of the colon	17	17 (100%)	11 (65%)	14 (82%)	12 (71%)	14 (82%)	10 (59%)
Non GI cancers	2	2 (100%)	2 (100%)	2 (100%)	1 (50%)	2 (100%)	0 (0%)

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dual upper and lower GI pathologies, with 55% having colon cancer in addition to a benign upper GI cause of anaemia.

With regards to referral categories it was evident that compliance with national guidelines was poor as many patients with alarm symptoms and anaemia were not referred urgently. Only 28% of dyspeptic patients who had anaemia were referred via an urgent pathway and only 22% of patients with dysphagia had an urgent review requested.

The commonest upper GI symptoms of heart burn and dyspepsia had an associated significant cause of anaemia in 48% and 50% of patients respectively. The incidence of heart burn and reflux have been reported to be 10% to 48% in the general population[30]. Dysphagia was only reported in 9 (7%) of the studied cohort. None of the upper GI symptoms had a significant difference in their distribution with respect to cause of anaemia, type of cancer or route of referral. Dyspepsia is nonspecific to organic conditions of the upper GI tract[107]. However, when detailed scoring of symptoms has been performed, it is able to identify patients at high risk of having significant pathology in the upper GI tract[108]. In contrast, the yield of cancer diagnosis from referrals of patients with alarm symptoms of upper GI tract has been low, with incidence ranging from 4% to 15% [74, 109].

The value of these symptoms in our anaemic population was not confirmed on univariate analysis.

High risk symptoms such as dysphagia and weight loss have been included as individual factors or as part of scoring systems to identify significant upper GI disease and cancer with some success, with an odds ratios of 2 for upper GI disease and 6 for cancer [31, 74, 110].

Change in bowel habit to loose motion or alternating loose motion and constipation were the commonest lower GI symptoms reported in this cohort. None of the lower GI symptoms had a significant relationship with a site of cause of anaemia except for constipation which has a tendency to be higher in patients with upper GI cancer (22%).

Loose motion and blood in the stool in the absence of perianal symptoms are high risk factors for significant lower GI disease with high predictive value for distal colonic cancer, colitis and large polyps [18, 27, 111, 112]. However their association with proximal colon cancer is poor. Loose motion has been included in a risk score by Fijten *et al* to predict colorectal cancer in general but does not differentiate if it is proximal or distal [12]. Majumdar *et al* demonstrated a 1.96 odds ratio of distal cancer when cluster symptoms (included loose motions) existed [11]. However, even in the presence of anaemia loose motions does not help predict PCC in the literature.

Weight loss was reported in 32 (25%) patients. The majority of these patients had a significant upper GI cause of anaemia. Only 19% of the patients with cancer in our cohort reported weight loss.

Blood profiles showed patterns that were correlated with causes of anaemia; patients with cancer had significantly lower haemoglobin and other blood indices compared with patients without cancer. The upper GI causes group had a tendency to have a higher MCV, MCH and lower RDW as compared with the lower GI causes group. This is explained by the longer silent phase of lower GI cancers and the potential of re absorption of heme from the upper GI tract slowing the progression of iron deficiency.

Iron studies, as well as B12 and folate, did not show significant differences between site causes of anaemia. However, patients with cancer did show a lower ferritin level compared with those without. This was even more pronounced in colonic cancers as compared to upper GI cancers.

Systemic causes of anaemia had a higher MCV, and MCHC with a lower RDW, MCH, and HCT. This pattern of anaemia reflects the common mechanism by which non-GI causes develop anaemia [49, 113, 114]. Erythropoiesis is deprived of iron as it is sequestrated in chronic inflammation response[49]. This iron deprived erythropoiesis commonly presents as normocytic (normal MCV), normochromic (normal MCHC)[48, 115] anaemia. The relatively normal RDW is likely due the slow development of anaemia in these patients

and chronicity of the condition which results in a homogenous population of red blood cells[116].

When assessing the pattern from GI causes of anaemia; it is evident that there is a pattern differentiating upper from lower GI causes.

In our univariate analysis colonic causes of anaemia had a lower MCV, MCH, MCHC and a higher RDW compared with upper GI causes. This is similar to the demonstrated pattern in the study of anaemia profiles in GI cancers (chapter 4).

It is evident from this study that the use of individual symptoms will not be successful in predicting the likely cause of anaemia or site of blood loss. In contrast, blood profile index, e.g. MCV or RDW, can allow a broader stratification of likely site of blood loss. Due to this the referral guidelines yield had a poor sensitivity and specificity for predicting site of cause of anaemia or for predicting cancer. The only measurable improvement in predicting cancer risk from referral guidelines[17, 24] , dyspepsia score[74], colorectal cancer risk scores [11, 12, 16] was achieved when combination of high risk symptoms and blood findings was performed. It is thus important to explore the predictive power of combining symptoms and blood indices to identify the site of blood loss and cancer risk.

Chapter 6

Development of streamlining tool for investigation of patients with anaemia

Development of streamlining tool for investigation of patients with anaemia

Abstract

DOH and BSG guidelines use symptoms and the presence of anaemia to classify patients at high risk of having serious GI pathology or cancer.

The yield of significant disease from urgent referrals is poor using these criteria due to the poor specificity.

In previous chapters of this it has been identified that GI symptoms are common and that they are not specific in identifying serious GI pathology causing anaemia. In contrast blood profiles have demonstrated a trend in identifying upper and lower GI pathology group.

This study aims to use the combination of symptoms and blood profiles to predict the likely site of cause of IDA and to develop a tool that could aid clinicians to quantify risk of site of blood loss and therefore guide in streamlining investigations.

A multistep logistic regression method was applied. Prediction scores of symptoms to predict likelihood of upper, lower GI and systemic causes of IDA was generated. Then the same was performed for blood profiles. Both scores were then combined to generate an overall score that combines symptoms and blood profiles in one tool. This score was then refined by

stepwise logistic regression analysis to reduce factors to generate a scoring tool that could be applied easily in the clinical setting.

Although upper GI symptoms have a positive correlation with the presence of upper GI pathology this did not reach statistical significance. ROC analysis demonstrated a good discriminatory power of the upper GI symptoms model with AUC of 0.69 (SE 0.05). The lower GI symptom regression model identified male gender and loss of appetite as positive predictors and young age, weight loss and NSAID use as negative predictors of lower GI pathology. The model had very good discriminatory power with AUC of 0.81 (SE 0.05). Blood indices regression models identified a high MCH as a predictor of upper GI pathology in females. In contrast to this, no combination of indices demonstrated an independent predictor of lower GI pathology. The upper GI blood model had AUC 0.77 (SE 0.05) and the lower GI blood model had AUC 0.77 (SE 0.06).

The combined scores model demonstrates significant prediction of the lower GI symptom and blood scores to a lower GI pathology. The discriminatory power was excellent with AUC of 0.91(SE 0.05). The combined upper GI model had an AUC of 0.77(SE0.05).

Using stepwise logistic regression analysis a clinical risk scoring tool was developed. The discriminatory power of the scores was good for upper GI

(AUC 0.72), very good for lower GI (AUC 0.86) and good for non-GI causes (AUC 0.69).

The clinical scoring tool mean scores were significantly higher for patients with pathology or cancer at the respective GI sites. The tool also identified patients with dual site pathology.

The scoring tool aided in predicting the likely site of pathology in patients referred with unexplained IDA, therefore aiding in streamlining patients to the appropriate investigation.

Introduction

The previous section assessed the profile of symptoms and blood indices in patients investigated for unexplained iron deficiency anaemia.

Analysis of each presenting symptom and its prediction of cause of anaemia failed to identify a strong predictor of cause of anaemia. This is due to the lack of specificity and high prevalence of these symptoms in the referred population. GI symptoms have been predictive of GI pathology [74, 80, 108], however the pathologies that cause chronic blood loss might not necessarily have pronounced symptoms.

Blood indices have demonstrate a trend to differentiate upper and lower GI pathology (chapter 4, chapter 5).

DOH and BSG guidelines use symptoms and anaemia broadly to classify patients at high risk of having cancer or GI pathology as a source of chronic blood loss.

This study assesses the use of a combination of detailed symptoms profile and blood indices in the prediction of the site of GI pathology, and to use that to develop a clinical tool that aids in classification of risk of site of pathology in unexplained IDA.

Methods

125 patients investigated for unexplained anaemia symptoms and blood indices profiles were analysed.

Univariate analysis of symptoms and blood profile indices in predicting site of blood loss was conducted in the previous chapter. Using that as a guide, multivariate analysis in the form of logistic regression was used to generate the prediction models. The investigation pathway of each patients follows an upper or lower GI assessment at first. Thus to reflect the clinical pathway of investigation, this study aimed to generate a tool that predicts the probability of cause of anaemia in one or more of three sites: upper, lower gastro-intestinal (GI) or non-GI causes of anaemia. It is also possible that a patient could have more than one site that could be contributing to the anaemia or have a significant pathology accounting for their symptoms. Due to this it would not be appropriate to use multivariate analysis to predict

three sites in one model (i.e. discriminate analysis). Hence logistic regression analysis was used to generate models using symptoms and blood indices to predict probability of each site (upper, lower or non-GI) separately [117]. The prediction score development followed a multistep process over 3 step processes: (see flow chart of model development in Appendix 3 and 4)

Step 1: Symptoms prediction of each site of pathology

Symptoms from each site of potential blood loss were entered in a logistic regression analysis to study the association of symptoms and the respective site. Constitutional symptoms such as loss of appetite and weight loss and use of NSAIDs or steroids are known to be associated with pathology at all three sites. They were included with respective site specific symptoms in the regression analysis for each site model.

In attempt to create a simpler model that is user friendly (with fewer symptoms), regression analysis with stepwise selection protocol was used. A factor was selected if the p value of the regression coefficient was lesser or equal to 0.2.

The regression coefficients were rounded to the nearest single decimal and then used to generate the weight of main symptoms. A risk score for each site based on symptoms was then generated.

Step 2: Blood Indices and prediction of each site of pathology

In a similar manner to symptoms, blood indices of interest were also entered in logistic regression to generate a score to predict the main site of possible cause of anaemia.

Using regression analysis with stepwise selection protocol a reduced prediction model to lower the number of factors was constructed. A factor was selected if the p value of the regression coefficient was lesser or equal to 0.2. The regression coefficients were rounded to the nearest single decimal and then used to generate the weight of main symptoms. A score was then generated for blood indices for each site.

Step 3: Combination scoring model using the symptom and blood models from steps 1 and 2

Both scores were combined in a logistic regression model to produce a probability prediction model for each site. Each patient then had a probability of having a condition causing anaemia at each site generated.

This stepwise approach was chosen to reflect current clinical practice. In a clinical setting the clinician would take history and examine a patient then based on their findings the risk of a cause of anaemia is estimated and the method of investigation determined. That risk was translated in an objective manner by using logistic regression to predict cause of anaemia using site

specific symptoms at first. Using blood indices to predict cause of anaemia was generated independent of symptoms. Symptoms and blood indices findings combined interaction is then assessed in a logistic regression model in the form of the combined model. This multistep approach will also adjust for the potential difference in type of correlation of factors and dependant outcome. It was assumed that all factor correlations with the outcome are a linear one. By separating symptoms and blood indices regression models, we have adjusted (normalised, or linearised) for the non-nonlinear relationship at each model. The final combined model will use linear independent factors (a symptom score and blood index score).

The final model reliability was assessed using the Receiver Operator Characteristic Curve (ROC) and Area Under Curve (AUC)[117].

Score cut off points for each site were selected to achieve a minimum sensitivity of 80%. When a score is above the chosen threshold it indicated the need for investigating the site accordingly.

Sensitivities, specificities and positive predictive values to cancer of the upper and lower GI tracts were also calculated.

Statistical analysis was conducted using t-test, paired t test, Mann-Whitney U test, chi-square test, Fisher exact test, McNemar test (paired chi-square test to measure disagreement) where appropriate.

Results

Step 1: Prediction of site of pathology using symptoms and a modelling of site symptom score:

Upper GI pathology symptom model:

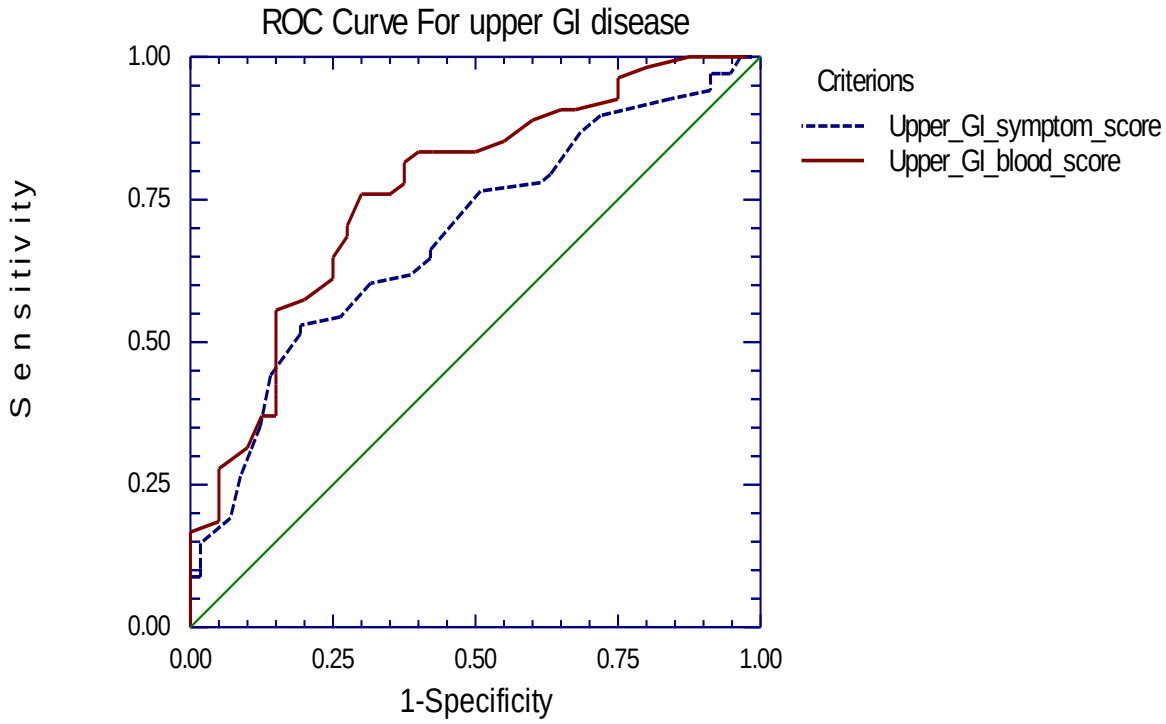
Symptoms that are specific to upper GI conditions and systemic symptoms associated with upper GI causes were entered in the logistic regression analysis (Table 6.1).

There was no significant relationship between upper GI symptoms, patient characteristics or demographics and upper GI causes of anaemia except for male gender. In the presence of anaemia, symptoms such as dyspepsia, dysphagia, nausea and use of NSAIDS, which are known to be a risk of presence of pathology in the upper GI tract, have been confirmed to be positively correlated with presence of a significant cause of anaemia in UGI tract. In contrast, older patients, male sex, reflux and vomiting have a trend to predict the absence of a significant upper GI cause of blood loss.

Table 6.1 Logistic regression of symptoms and upper GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	1.70489	1.316018	0.195151
Age	-1.65E-02	1.77E-02	0.351047
Male gender	-0.86785	0.410032	0.034298
Heart burn or reflux	-0.16156	0.470437	0.731286
Dyspepsia	0.328875	0.559869	0.556926
Epigastric or RUQ Pain	-6.86E-02	0.770992	0.929098
Nausea	0.39752	0.944819	0.673948
Vomiting	-0.98507	1.076923	0.360346
Dysphagia	1.168429	0.904587	0.196471
Previous gastric surgery	16.35293	3093.51	0.995782
Melena or Hematemesis	6.92E-02	0.798944	0.930958
Weight loss	-0.29485	0.521854	0.572069
Loss of appetite	-0.2613	0.572826	0.648277
NSAIDS or Aspirin	0.327141	0.410104	0.425043
Steroids	-17.828	5439.527	0.997385
Warfarin	0.403977	0.823349	0.623673

Figure 6.1 : Receiver Operating Characteristic Curve (ROC) for upper GI symtpoms and blood score prediction model



The upper GI cause probability model based on symptoms was generated using all factors entered in the logistic regression model. This had a discriminatory power that was good with an area under receiver operating characteristic curve (AUC) of 0.69(SE 0.05)(Figure 6.1).

Lower GI pathology symptom model:

Table (6.2) lists the factors entered in lower GI cause prediction model. Older age, absence of weight loss and use of NSAIDS were the only significant predictors of lower GI pathology.

In contrast to what has been reported in literature, change in bowel habit to loose motions or increased frequency was not a positive predictor of significant lower bowel pathology. However loss of appetite and male gender had a tendency to predict a significant pathology.

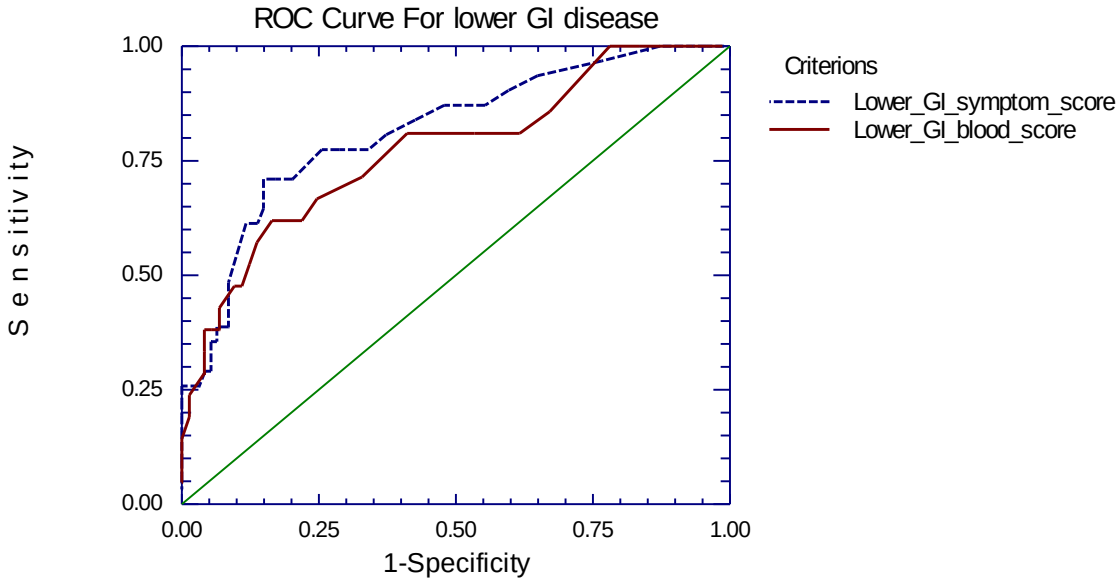
As has been noted in univariate analysis in earlier chapter, NSAID use had a trend to protect from significant lower GI pathology.

The model generated for lower GI pathology had a very good discriminatory power with AUC of 0.81(SE 0.05) (Figure 6.2)

Table 6.2 Logistic regression of symptoms and Lower GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	-5.37213	1.897461	0.004637
Age	6.83E-02	2.61E-02	0.008783
Male gender	0.145492	0.514794	0.777467
Blood in stool	-0.57284	0.843355	0.496988
Change in bowel habits to loose motion or alternating	-0.81231	0.634027	0.200126
Slime in stool	1.028066	1.031938	0.31913
Increased frequency of stool	-0.34665	1.214421	0.775306
Constipation	-0.97988	1.265433	0.438727
Abdominal pain	0.890447	0.657207	0.175451
Inflammatory Bowel Disease	-2.57583	1.630615	0.114183
History of colonic polyps	1.316398	1.819618	0.469405
Family history of colorectal cancer	0.964861	1.233193	0.433974
RIF pain	-8.24E-02	1.395314	0.952926
Weight loss	-2.13843	0.896713	0.017091
Loss of appetite	1.546345	0.904979	0.087505
NSAIDS or Aspirin	-1.72756	0.578502	0.002824
Steroids	-18.761	3299.24	0.995463
Warfarin	0.638578	0.952169	0.50244

Figure 6.2: Receiver Operating Characteristic Curve (ROC)for Lower GI Symtpoms and Blood Score prediction model



Non GI causes of anaemia prediction model:

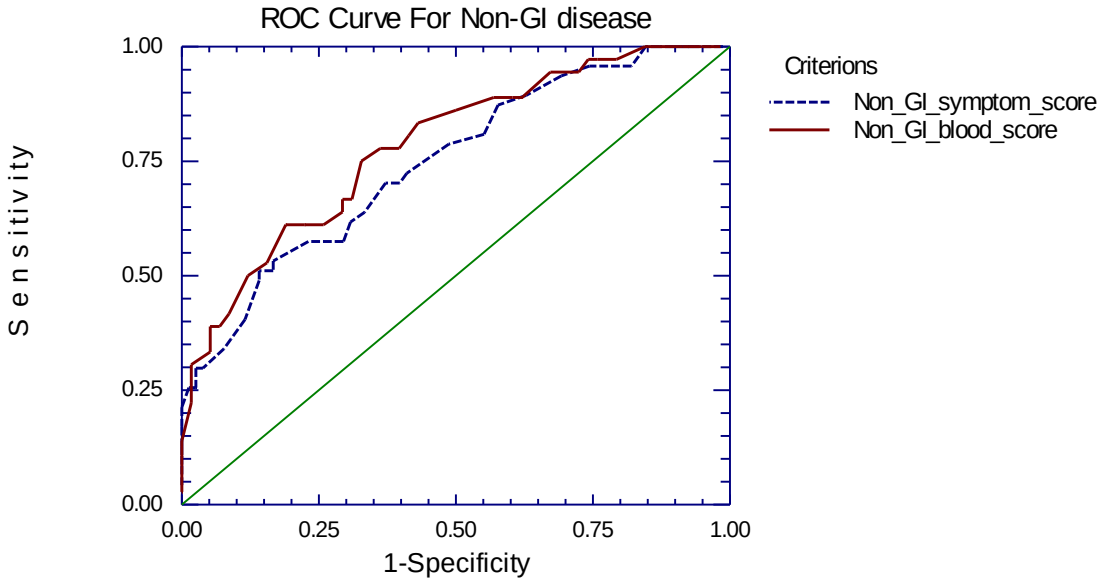
None of the systemic symptoms had a significant prediction of non-GI pathology. Being female was a significant independent predictor of non-GI causes (Table 6.3).

The model for non-GI causes of anaemia had a good discriminatory power with an AUC of 0.75(SE 0.05)(Figure 6.3).

Table 6.3 Logistic regression of symptoms and non-GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	0.22679	1.32046	0.863634
Age	-2.28E-02	1.86E-02	0.22154
Male gender	1.065562	0.449875	0.017857
Weight loss	0.817102	0.558968	0.143795
Loss of appetite	-0.56341	0.66207	0.394782
Abnormal nails	18.48434	5439.527	0.997289
Sore tongue	-14.2686	5439.527	0.997907
Night sweats	-34.5622	6624.828	0.995837
Pruritus	-16.6919	3727.765	0.996427
Joint pain	-0.4118	0.741615	0.578706
Rheumatoid Arthritis	2.602973	1.74179	0.135065
Chronic Renal Failure	0.914686	0.90113	0.310085
NSAIDS or Aspirin	0.495769	0.448692	0.269195
Steroids	20.4224	5439.527	0.997004
Warfarin	-1.88312	1.211445	0.120079

Figure 6.3: Receiver Operating Characteristic Curve (ROC) for Non- GI symtpoms and blood score prediction model



Step 2: Prediction of site of pathology using blood indices and modelling of blood results score:

Logistic regression was used to assess independent predictors of site of cause of anaemia using blood indices, iron and ferritin. Age and sex of patients were entered in the model due their independent effect on variation of normal values of used blood indices.

Tables 6.4, 6.5 and 6.6 list the results of regression with respect to each site. Female gender and high MCH were significant predictors of an upper GI cause of anaemia. Low MCV had a tendency to predict an upper GI cause. High serum iron and low ferritin were associated with a tendency to find an upper GI cause of anaemia (table 6.4).

Using all blood indices, serum iron, ferritin, gender and age in a prediction model had good discriminatory power with AUC 0.77(SE 0.05) (Figure 6.1)

Table 6.4 Logistic regression of blood indices and iron studies and upper GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	35.02379	50.92329	0.491594
AGE	-1.12E-02	2.36E-02	0.635342
Sex	-1.77598	0.570358	0.001847
Hb	-0.69997	0.494078	0.156564
RBC	0.364344	2.787449	0.896006
HCT	2.296068	1.705369	0.178181
MCV	-1.299	0.664429	0.050576
MCH	4.294783	1.886189	0.022788
MCHC	-0.13582	0.166095	0.413524
RDW	5.21E-03	0.117015	0.964458
Iron	4.13E-02	3.26E-02	0.204449
Ferritin	-2.73E-03	3.01E-03	0.363573

None of the indices were a significant predictor of lower GI pathology.

However, relatively high haemoglobin and low haematocrit had a tendency to predict lower GI causes (Table 6.5).

Based on logistic regression model the discriminatory power was good with AUC of 0.77(SE 0.06) (Figure 6.2).

Table 6.5 Logistic regression of blood indices and iron studies and lower GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	88.08009	65.55109	0.17905
Age	8.53E-03	2.82E-02	0.76246
Sex	0.349876	0.627678	0.577246
Hb	1.384272	0.715906	0.053163
RBC	-2.30523	4.515726	0.609709
HCT	-4.15305	2.416626	0.0857
MCV	0.789414	0.78913	0.317137
MCH	-2.85955	2.2342	0.200581
MCHC	-0.25759	0.213908	0.228507
RDW	0.128121	0.136513	0.347975
Iron	3.54E-02	3.11E-02	0.255083
Ferritin	6.69E-04	3.51E-03	0.849007

Being male with high MCV and low MCH was significantly associated with non-GI causes of anaemia.(Table 6.6). The AUC of the non-GI model was 0.78(SE 0.05)(Figure 6.3)

The discriminatory powers of all prediction sub scores are listed in table 6.7

Table 6.6 Logistic regression of Blood indices and iron studies and non-GI causes of anaemia

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	-73.24	59.46578	0.218086
Age	-0.0211	2.40E-02	0.378007
Sex	1.484863	0.542451	0.006194
Hb	0.417138	0.51347	0.416568
RBC	1.661527	3.308955	0.615576
HCT	-1.62495	1.792964	0.364781
MCV	1.468567	0.739989	0.047191
MCH	-4.32203	2.060449	0.035939
MCHC	0.225358	0.187308	0.228922
RDW	-0.14945	0.134587	0.266808
Iron	-0.02066	3.18E-02	0.515958
Ferritin	0.00342	2.99E-03	0.252775

Table 6.7 Discriminatory powers as assessed by Area Under ROC Curve (AUC) of symptoms and blood score models for prediction of respective sites.

Prediction Model	AUC	SE
Upper GI symptom score	0.686533	0.047
Upper GI blood score	0.765278	0.04824
Lower GI symptom score	0.816232	0.049423
Lower GI blood score	0.77332	0.064244
Non- GI symptom score	0.746045	0.04726
Non-GI Blood score	0.783285	0.05122

Step 3: Combination scoring model using the symptom and blood models from steps 1 and 2 to predict probability of cause of anaemia at each site.

Each patient has a probability of an upper GI, lower GI, and non-GI cause of anaemia. Because each site has its own independent symptom and blood profile, a risk score for each site is needed by combining the respective site symptom and blood profile score models in a logistic regression model. (Tables 6.8, 6.9, 6.10)

Table 6.8 Logistic regression of upper GI symptom and blood scores models to develop the upper GI cause probability prediction model.

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	-3.28263	0.963322	0.000655
Upper GI symptom Score	2.256121	1.631184	0.166629
Upper GI Blood Score	4.182976	1.200895	0.000495

Table 6.9 Logistic regression of lower GI symptom and blood scores models to develop the lower GI cause probability prediction model.

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	-5.0211	0.980781	0
Lower GI symptom Score	7.227287	1.864614	0.000106
Lower GI Blood Score	6.473686	1.807623	0.000342

Table 6.10 Logistic regression of non-GI symptom and blood scores models to develop the non-GI cause probability prediction model.

Variable	Regression Coefficient	Standard Error	*p value*
Intercept	-3.43909	0.692354	0.000001
Non- GI symptom Score	3.702015	1.368322	0.00682
Non-GI Blood Score	3.754554	1.256895	0.002816

Except for upper GI symptoms, it is evident that site symptoms and blood score components are significant predictors of significant causes of anaemia at relevant GI sites.

The ROC curves for the full models for each site are presented in figures 6.4, 6.5 and 6.6.

Figure 6.4: Receiver Operating Characteristic Curve (ROC) for the upper GI cause probability model

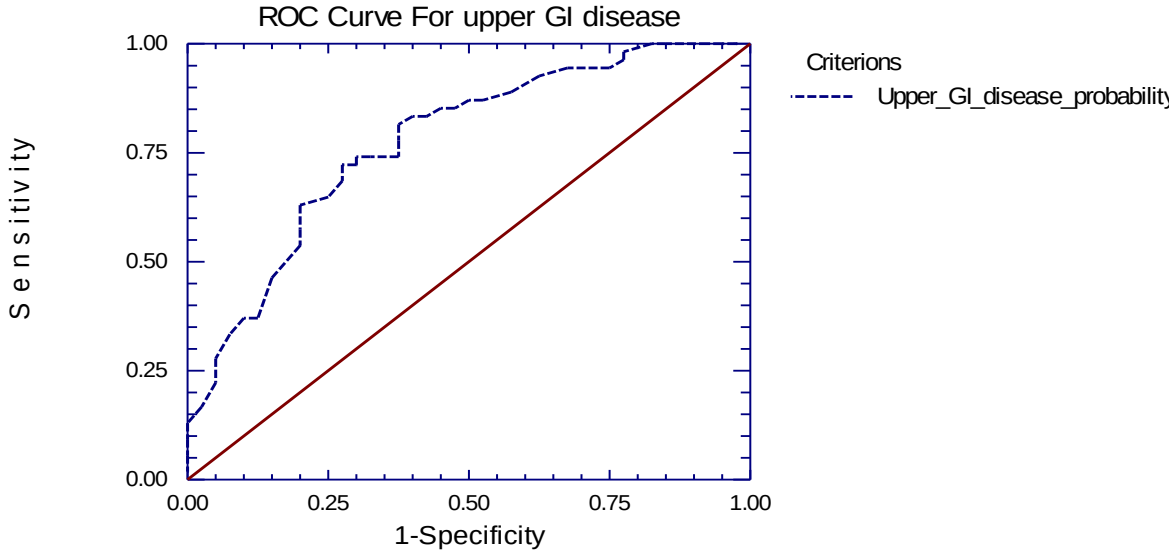


Figure6.5: Receiver Operating Characteristic Curve (ROC) for the lower GI cause probability model

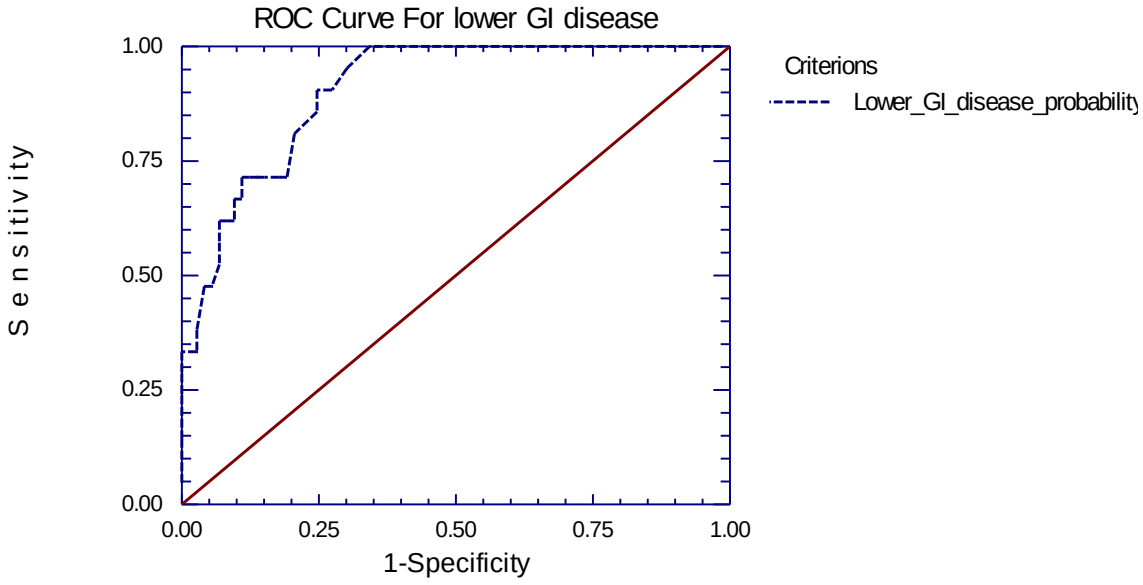
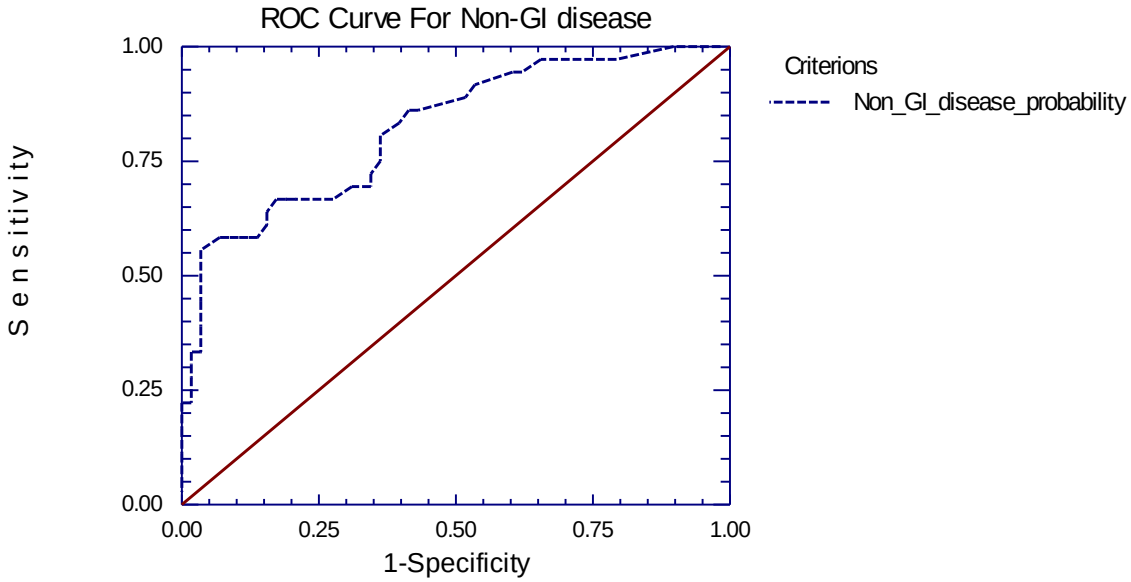


Figure 6.6: Receiver Operating Characteristic Curve (ROC) for the Non-GI cause probability model



Lower GI site cause probability model had the highest discriminatory power with an AUC of 0.91(SE 0.05) followed by non GI cause probability model with an AUC of 0.82(SE 0.05) and upper GI with AUC of 0.77(SE 0.05) (Table 6.11).

Table 6.11 Discriminatory powers as assessed by Area Under ROC Curve (AUC) of the full score models for prediction of respective sites.

Prediction Model	AUC	SE
Upper GI cause probability model	0.774306	0.047407
Lower GI cause probability mode	0.90574	0.045358
Non-GI cause probability mode	0.821839	0.047375

Reduced scoring model

To create a score that could be easily used, stepwise selection logistic regression was used to generate a model with fewer elements to predict site of cause of anaemia.

Table 6.12 demonstrates the results of the selected symptom factors and blood indices with respect to each site.

For upper GI factors, being female and having dysphagia in the presence of anaemia were strong predictors. From lower GI factors, age, change in bowel habit to loose motions, loss of appetite, and use of NSAIDS were selected.

For non- GI causes being male, weight loss, warfarin use, chronic disease of rheumatoid arthritis and chronic renal failure were selected.

Hematocrit, MCV and MCH were selected for all sites, haemoglobin and serum iron levels were selected for GI causes and MCHC for lower GI and systemic causes. RDW was only scored for non-GI cause.

Using the regression coefficients weights were generated for each factor. A final symptom and blood score was calculated. Both scores were entered in a logistic regression model to calculate probability of each site having a significant cause of anaemia (Table 6.13, 6.14).

Table 6.12: Stepwise regression analysis of symptoms and blood indices with respect to site of cause of anaemia.

Site of cause of Anaemia	Variable	Regression Coefficient	Standard Error	*p value*
	Intercept	0.497252	0.271806	0.067334
	Dysphagia	1.129249	0.833485	0.175465
	Male Sex	-0.75341	0.369236	0.041304
	Intercept	-4.52689	3.803218	0.233936
Upper GI	MCH	3.602479	1.401863	0.010176
	Male sex	-1.66998	0.540062	0.001987
	Hb	-0.93545	0.350117	0.007544
	Iron	4.63E-02	3.22E-02	0.150967
	HCT	3.06249	1.108832	0.005746
	MCV	-1.12229	0.440005	0.010753
	Intercept	-4.4055	1.640754	0.007252
	Age	5.80E-02	2.25E-02	0.010046
	NSAIDS	-1.56121	0.521967	0.002781
	Weight loss	-1.06482	0.620518	0.086158
	Change in bowel habits to loose motions	-0.68852	0.514419	0.180751
	Loss of appetite	1.546345	0.904979	0.087505
Lower GI				
	Intercept	79.217	58.34305	0.174534
	Iron	4.15E-02	2.79E-02	0.137544
	MCHC	-0.25198	0.192352	0.190189
	Hb	1.522903	0.646263	0.018449
	MCH	-3.56346	1.978182	0.071643
	HCT	-4.84031	1.99553	0.015284
	MCV	1.119214	0.620663	0.071348
	Intercept	-1.28112	0.341184	0.000173
	Warfarin	-1.2162	0.885015	0.169375
	Male sex	0.96485	0.407127	0.017793
	Weight loss	0.607706	0.449715	0.176595
	RA	2.308212	1.341808	0.085391
	CRF	1.644989	0.928771	0.076537
Non GI				
	Intercept	-94.8131	46.16448	0.039994
	MCHC	0.318784	0.150913	0.034655
	Male sex	1.456961	0.535447	0.006508
	RDW	-0.19852	0.12514	0.112662
	MCH	-3.7414	1.819083	0.03971
	HCT	-0.12332	8.02E-02	0.124226
	MCV	1.189748	0.572832	0.037805

Lower GI probability score had a high discriminatory power but was reduced from the full model. In contrast to the full model, upper GI probability score had higher discriminatory power than the non-GI cause power (Table 6.15, Figures 6.7, 6.8, 6.9).

Table 6.13 Scoring tool and probability equation for generation of the reduced site prediction model.

	UGI Score	LGI Score	Non GI Score
AGE		Age x 0.05	
Male gender	-1		1
Change in bowel habit to loose motion		-1	
Dysphagia	1		
Weight loss		-1	1
Loss of appetite		1.5	
NSAIDS		-1.5	
Warfarin			-1
PMH of RA			2
PMH of CRF			1.5
Total symptom score (SS)			
Male gender	-1.5		1.5
Hb (g/l)	X -1	X 1.5	
HCT (%)	X 3	X -5	X -1.2
MCV(fl)	X -1	X 1	X 1
MCH(pg)	X 3.5	X -3.5	X -4
MCHC (g/l)		X -0.25	X 0.3
RDW			X -0.2
Iron (µmol/l)	X 0.05	X 0.05	
Total blood score (BS)			
Y	**-0.45+(0.99xSS)+(0.32x BS)**	**43+(1.47xSS)+(0.51xBS)**	**0.095+(0.89xSS)-(0.049xBS)**
Probability for site 1/[1+Exp(-y)]			

Table 6.14 Logistic regression of site specific symptom score and blood component score with respect site of cause of anaemia.

Site of cause of Anaemia	Variable	Regression Coefficient	Standard Error	*p value*
Reduced Upper GI score	Intercept	-0.45308	0.813279	0.577454
	Upper GI symptom score	0.987839	0.445928	0.026743
	Upper GI blood score	0.318355	0.192558	0.098272
Reduced Lower GI score	Intercept	43.78119	13.47099	0.001154
	Lower GI symptom score	1.474883	0.395772	0.000194
	Lower GI blood score	0.514304	0.145567	0.000411
Reduced non GI score	Intercept	9.50E-02	1.080741	0.929934
	Non-GI symptom score	0.886059	0.260064	0.000657
	Non- GI blood score	-4.88E-02	3.62E-02	0.176628

Table 6.15 Discriminatory power assessed by Area Under ROC Curve (AUC) of the reduced models for prediction of cause of anaemia at respective sites.

Prediction Model	AUC	SE
Reduced upper GI prediction score	0.721	0.05
Reduced lower GI prediction score	0.862	0.05
Reduced non-GI prediction score	0.694	0.05

Figure 6.7: Receiver Operating Characteristic Curve for the reduced upper GI prediction model.

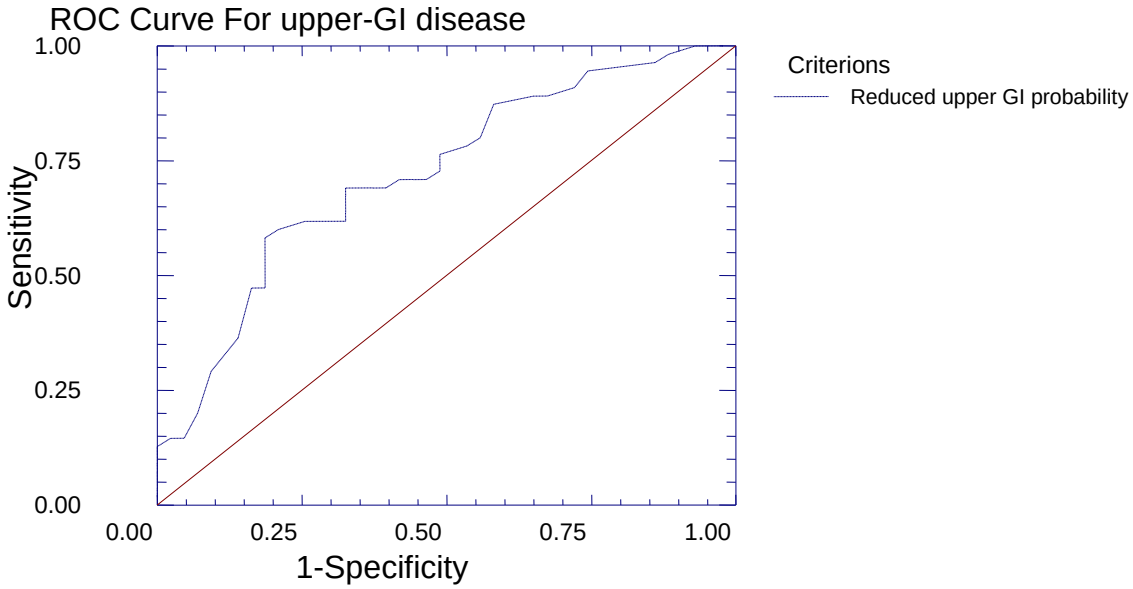


Figure 6.8: Receiver Operating Characteristic Curve for the reduced lower GI prediction model

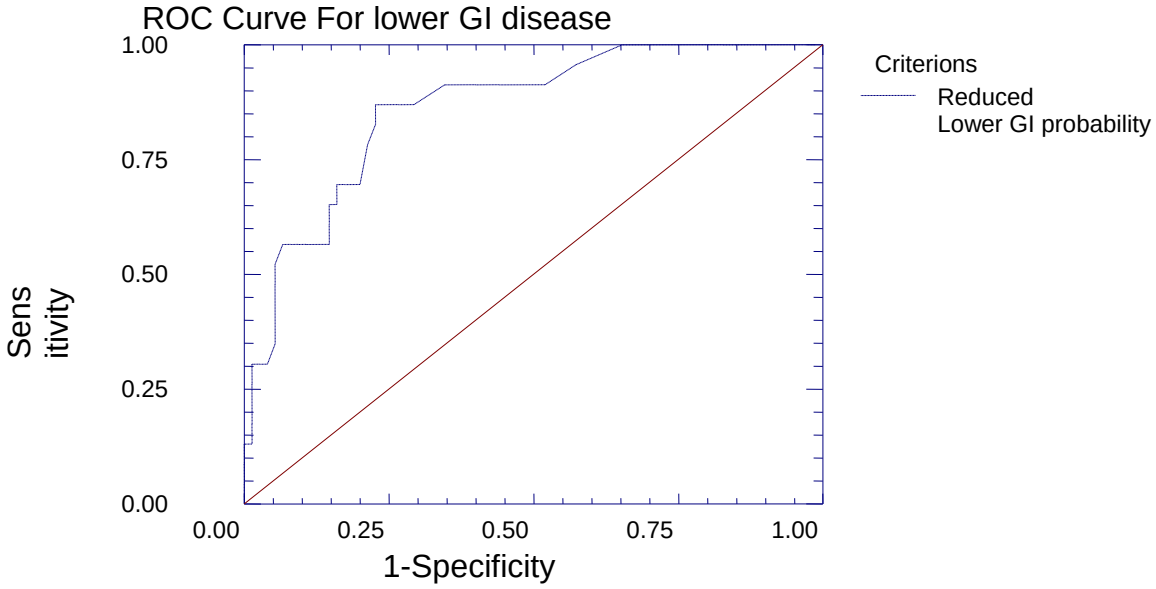
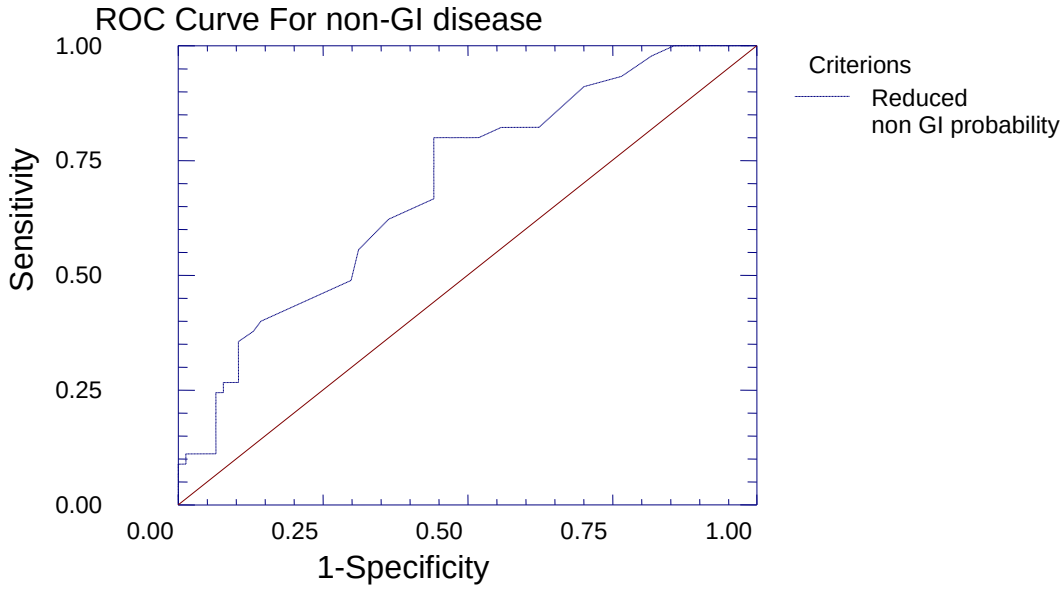


Figure 6.9: Receiver Operating Characteristic Curve for the reduced non- GI prediction model.



Diagnostic values for the prediction model.

Average scores of diagnosis groups

Table 6.16 summarises the average scores of all prediction models and patients diagnosis groups. The average scores of both upper GI full model and the reduced score were significantly higher in patients who had upper GI conditions as the sole cause of anaemia or in combination with colonic or systemic disease (Table 6.16, Figure 6.10).

Lower GI full model and lower GI reduced model also had a significantly higher mean scores in patients who had lower GI conditions (ANOVA, $p<0.01$). Furthermore, when there was no significant colonic condition causing anaemia the average scores were very low (Figure 6.10).

Patients with systemic conditions scored significantly high on the non GI models.

Table 6.16: Average scores of the prediction models and patient diagnosis groups.

	Average prediction scores(Standard Error)					
Site of cause of anaemia	**Full Upper GI score**	**Reduced Upper GI score**	**Full Lower GI score**	**Reduced Lower GI score**	**Full Non GI score**	**Reduced non GI score**
Upper GI disease	71(3)	65(3)	12(3)	17(3)	26(4)	33(2)
Systemic causes	43(4)	47(3)	15(4)	14(4)	58(4)	45(3)
Colonic disease	45(7)	49(5)	51(7)	48(6)	34(7)	32(4)
Upper GI and colonic disease	63(7)	62(6)	64(8)	54(7)	19(8)	31(5)
Upper GI and systemic disease	48(9)	42(8)	5(10)	5(9)	68(10)	55(7)
Colonic and systemic disease	50(15)	60(12)	54(16)	41(15)	47(16)	30(11)
Upper GI, colonic and systemic disease	66(21)	74(17)	50(22)	57(21)	24(23)	18(16)
ANOVA *p values*	<0.001	<0.001	<0.001	<0.001	<0.001	0.001

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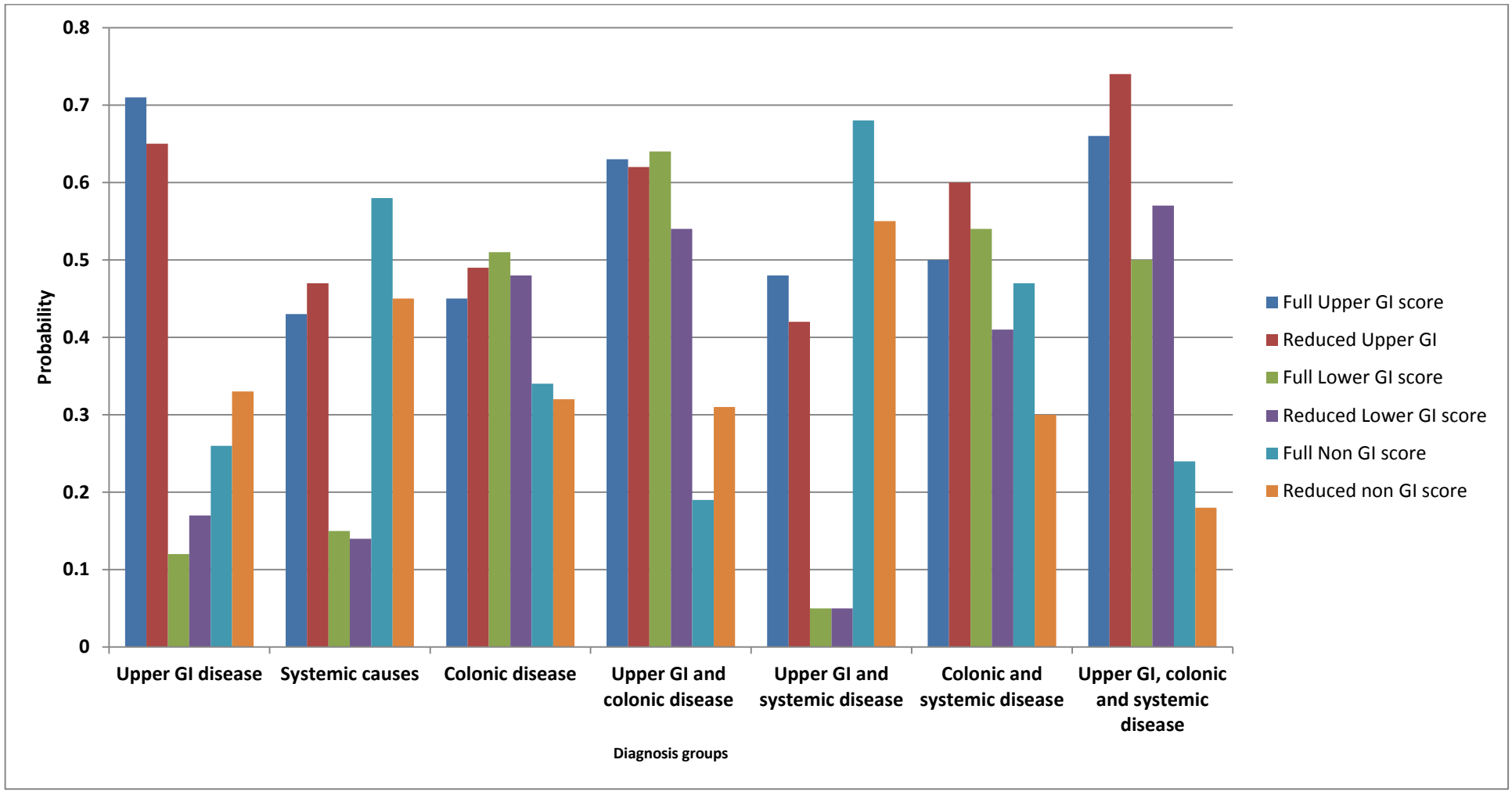
Figure 6.10: Average scores of prediction models and patient's diagnosis groups.



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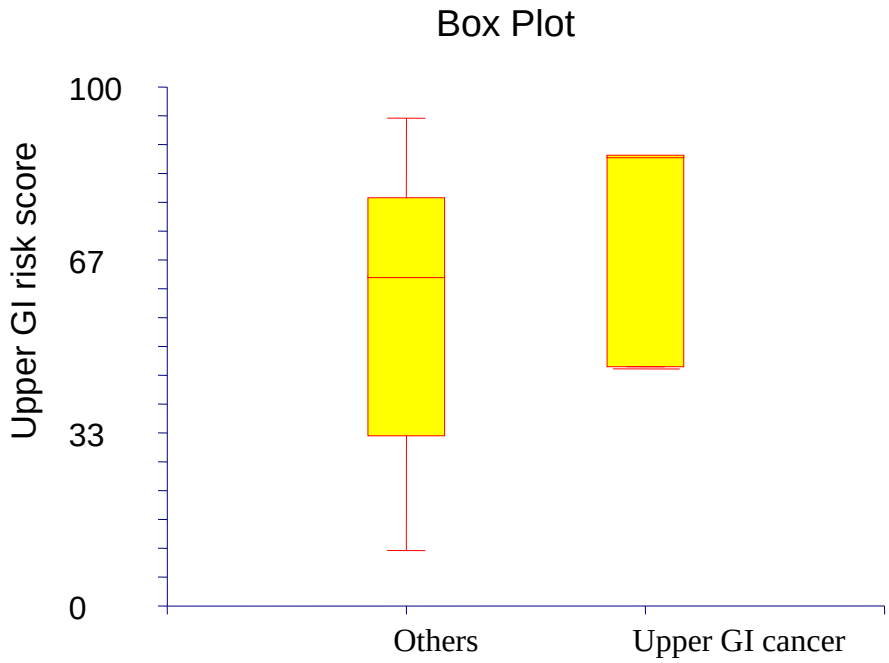
Patients with upper GI cancers had a higher upper GI full model score than other patients although not reaching statistical significance (Table 6.17, Figure 6.11).

Table 6.17: Average scores of upper GI prediction models and upper GI cancer

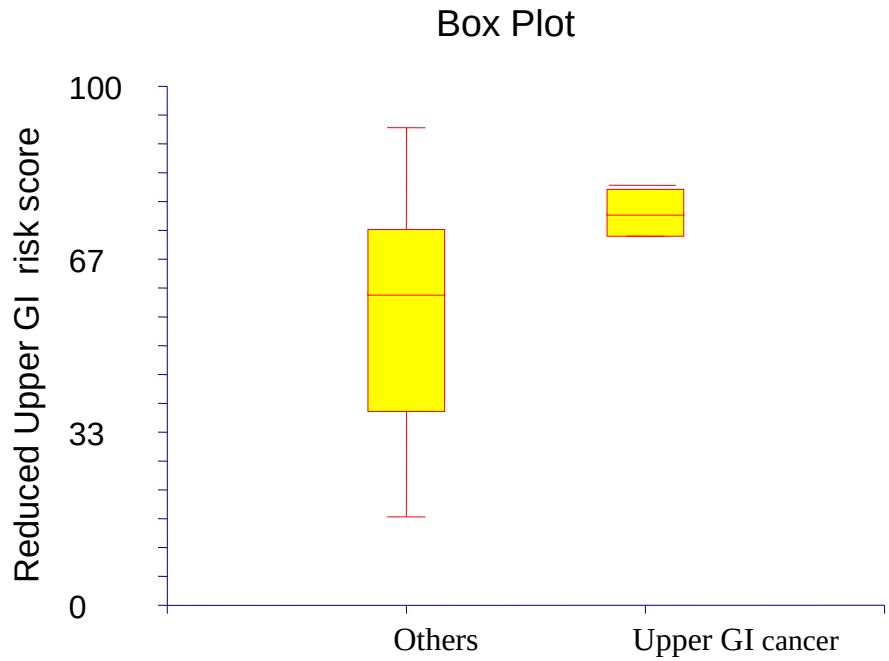
Group	Full Upper GI score	Reduced Upper GI score
Upper GI cancer	73(23)	76(5)
Others	57(24)	56(19)
p value	***0.16***	***0.04***

Figure 6.11: Box plot of full upper GI prediction score and upper GI cancer.



The reduced upper GI model however, demonstrated a significant difference in average scores between upper GI cancers and other patients (Table 6.17, Figure 6.12)

Figure 6.12: Box plot of reduced upper GI prediction score and upper GI cancer.



There was a significance difference between average scores of lower GI cancers and other patients when using both lower GI full prediction and reduced prediction models (Table 6.18, Figures 6.13, 6.14).

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Table: 6.18: Average scores of lower GI prediction models and lower GI cancer.

Group	**Full Lower GI score**	**Reduced Lower GI score**
Lower GI cancer	53(29)	55(27)
Others	18(26)	19(22)
p value	***0.0001***	***0.00003***

Figure 6.13: Box plot of full lower GI prediction score and lower GI cancer.

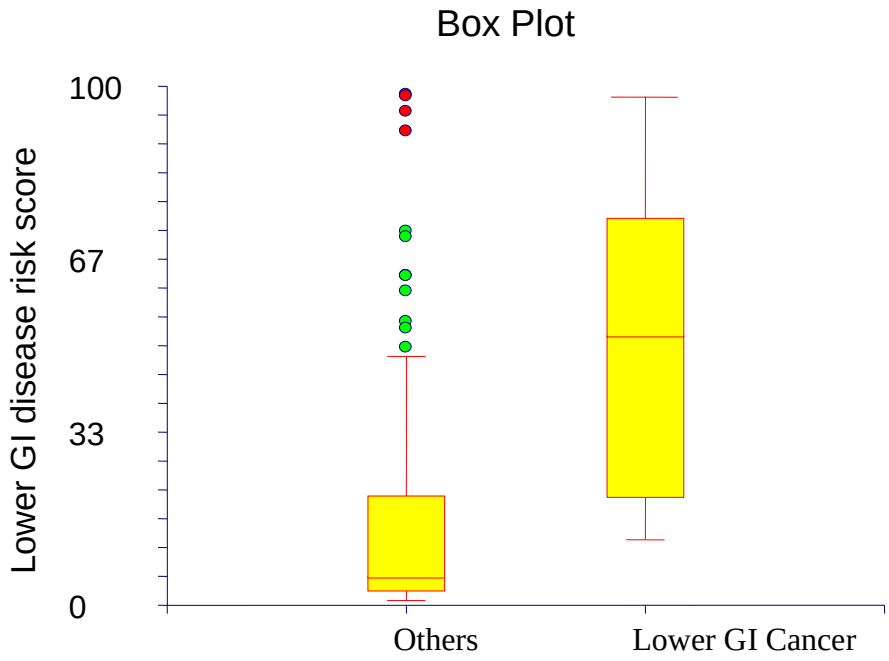
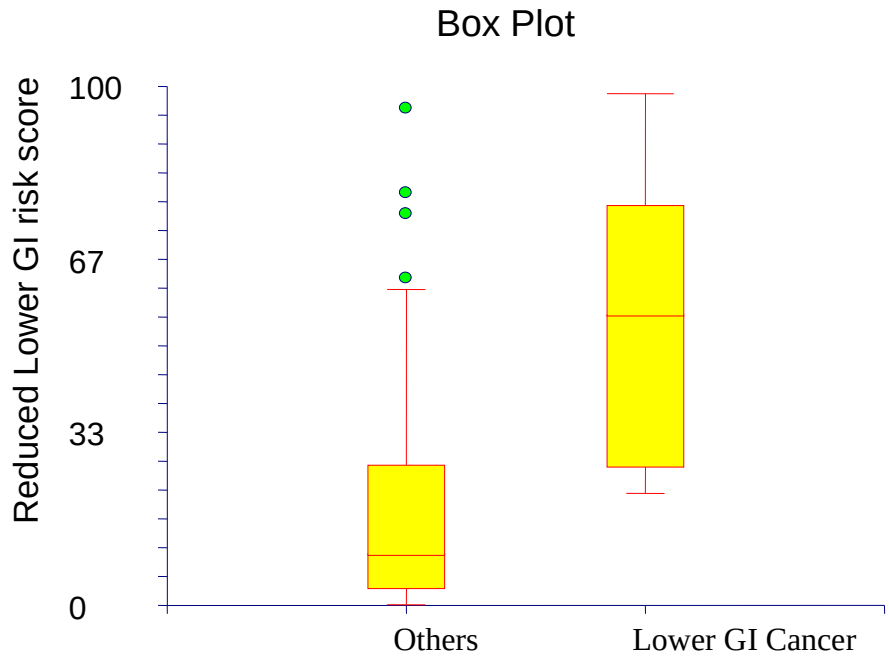


Figure 6.14: Box plot of reduced lower GI prediction score and lower GI cancer.



Efficacy of referral guidelines and prediction scores in identification of significant causes of anaemia and GI cancer.

Thresholds for investigation of the prediction scores were determined using the ROC curve with a minimum sensitivity of 80% to the cause of anaemia respective to site. For UGI full and reduced prediction model a probability of upper GI disease of ≥ 40 was regarded as a threshold for urgent assessment of the upper GI tract.

For lower GI prediction models a probability of ≥15 using the full lower GI model and ≥20 using the reduced prediction model was regarded as threshold for urgent assessment of the lower GI tract. A systemic cause of anaemia was likely when the full non GI model scored ≥23 and the reduced non GI model scored ≥ 30.

Table 6.19 compares the diagnostic values of prediction models, DoH urgent referral criteria and BSG threshold of high risk anaemia with regard to causes of anaemia and GI cancers.

Both upper GI prediction models were significant in detecting upper GI causes of anaemia at threshold probability of 40. Using these thresholds, upper GI causes of anaemia would have been detected in 80% and 85 % of patients when the full upper GI model and the reduced models were used respectively. DoH and BSG referral criteria did not show a significant

prediction of upper GI causes of anaemia with only 32% and 40% respectively meeting the criteria.

The upper GI prediction models had a significantly higher sensitivity to upper GI causes of anaemia and referral rates than DoH and BSG criteria (McNemar test, *p<0.001).* There was no significant difference between the two upper GI models in sensitivity and referral rates.

All upper GI cancers (100%) scored above the model score thresholds. 75% of the upper GI cancers met the DoH and BSG referral criteria. This difference however, did not reach statistical significance

The lower GI full model at a threshold score of 15 and the reduced model at a score of 20 were both significant predictors of lower GI causes of anaemia. DoH criteria were significant in predicting lower GI causes with 55 % of lower GI causes meeting the DoH referral criteria. BSG criteria failed to show a significant detection of lower GI causes of anaemia. The models were more sensitive to lower GI causes than DoH and BSG Criteria (McNemar test, *p<0.05)*. All lower GI models had a higher sensitivity to lower GI cancers than the DoH and BSG criteria (Table 6.19), however, this was not statistically significant (McNemar test, *p>0.08*)

Table 6.19 Efficacy of scoring models and referral criteria and main site of anaemia and GI cancer.

Cause of anaemia	Criteria	Sensitivity	Specificity	Positive predictive value	Referral Rate
UGI causes of anaemia	**Full upper GI model score ≥40**	85	55	72	68
	Reduced upper GI model score ≥40	80	44	65	69
	DoH	32	58	48	37
	BSG	40	72	63	34
UGI cancers	**Full upper GI model score ≥40**	100	33	5	68
	Reduced upper GI model score ≥40	100	31	4.4	69
	DoH	75	64	7	37
	BSG	75	67	7	34
Lower GI causes of anaemia	**Full lower GI model score ≥15**	91	75	51	39
	Reduced lower GI model score ≥20	87	77	54	38
	DoH	55	69	37	37
	BSG	48	70	35	34
Lower GI cancer	**Full lower GI model score ≥15**	91	68	27	39
	Reduced lower GI model score ≥20	100	70	32	38
	DoH	71	69	26	37
	BSG	71	71	28	34

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Discussion

Patients referred for investigation of unexplained anaemia to a dedicated clinic had their symptoms and blood profiles collected in a systematic manner and analysed.

Using these symptom profiles and blood indices, an analysis of prediction value to the cause of anaemia was performed. This cohort of patients had their gastrointestinal tract investigated and a final diagnosis was made in all patients after a minimum period of follow up of 1 year.

The aim of this section was to establish a risk score that predicts the likelihood of a cause of anaemia from the upper, lower gastrointestinal tract or systemic causes of blood loss. The methodology chosen was multivariate analysis using logistic regression to predict individual sites of blood loss using site specific symptoms and general blood indices profile. This method has been used in clinical prediction models extensively [81, 82, 118-123]. A multistep approach was then chosen to adjust for the variation in the degree of linearity and slope of correlation between the independent factors and the outcome it also reflects the clinical pathway of patients.

Symptoms and blood indices correlate differently in relation to cause of anaemia. This is why it was important to perform two independent regression analyses, prediction of site specific symptoms to site of cause of anaemia and prediction of blood indices to site of cause of anaemia.

Furthermore the data type was binary in the case of symptoms and continuous in the case of blood profiles. Hence separating the two would allow the regression analysis to handle the variables better. Each generated model has thus fitted the respective factors in a relationship that is a linear model which transformed the data to a continuous variable. That allowed for a better representation of all selected factors, and better regression to predict the site of cause of anaemia [117, 124].

Gender has influence within both the symptoms and blood profiles. It is has been identified that the incidence of symptoms in the presence of an upper or lower GI pathology is significantly different between males and females.[74, 108, 111] On the other hand, blood profiles are affected differently between genders. Firstly the anaemia threshold is different, hence a Hb value of 10 in males is regarded as a significant anaemia but only mild in females. This in turn will effect the other indices too (MCV etc.). It is more concerning if a male patient presented with symptoms, weight loss and haemoglobin of 10 than if a female presents with weight loss and a similar haemoglobin value.

Symptom models:

The first step of the generation of the model confirmed the poor predictive value of symptoms. Both the full model and the stepwise selection model (reduced model) failed to identify a strong symptom predictor of site of

disease. Traditionally recognised high risk symptoms such as dysphagia, loss of appetite and weight loss have demonstrated a tendency to correlate in a positive or negative manner with disease sites. This is could be explained by the high incidence of non-specific symptoms in this cohort and the rarity of clinically significant symptoms such as dysphagia which is a result of rare conditions causing anaemia such as oesophageal cancer, or peptic strictures. The use of these symptoms in referral guidelines therefore would not aid in identifying high risk patients in the majority of cases, and will only yield true positives in a few cases. This poor specificity will result in a high referral rate, i.e. numbers of patients requiring investigation will be high.

In our proposed final clinical tool, only dysphagia for upper GI had a positive influence on the risk score, for lower GI loss of appetite had a positive influence on risk, loose motions and weight loss had a negative influence. The negative effect of loose motion in predicting lower GI causes is surprising. Loose motions are associated with high incidence of colon cancer and IBD[12, 80]. Both conditions cause anaemia. Distal colon cancer however is more frequent, does not commonly present with anaemia, and it is commonly associated with loose bowel motions [5, 125]. Proximal colon cancer on the other hand presents with anaemia and does not have primary symptoms except in less than 5% of patients. This would explain the lack of positive association with anaemia and loose motions in lower GI conditions

causing anaemia identified in this cohort. Only 2 distal colonic cancers, and 2 IBD patients out of the 31 patients with colonic causes of anaemia where identified. The remaining colonic causes do not correlate with loose motions. Hence using loose motions with anaemia in classifying patients at high risk of significant cause will have a false positive rate. In fact the majority of patients with anaemia and colonic causes will have no change in bowel habits to loose motions.

The use of drugs such warfarin and aspirin, the past medical history of rheumatoid arthritis, chronic renal failure, and presence of weight loss predicted a non-GI cause of anaemia.

Blood indices model:

It is important to note that all these patients are anaemic at referral time. It is the degree of anaemia that is used to predict the likely cause of blood loss. Chapter 3 outlined different patterns of anaemia when cancer was the cause it was in the upper GI tract compared with proximal colon cancer. This pattern was attributed to the ability of the blood loss from the upper GI tract to be reabsorbed in the small bowel, and that overt blood loss from the upper GI tract will present with an acute picture rather than chronic loss (i.e. mildly low or normal MCV vs. low MCV).

In this cohort none of the patients presented acutely with blood loss. All patients had a slow occult source of blood loss.

The final clinical model identified that blood loss from lower GI causes had a milder anaemia, but ultimately a defective haemoglobin synthesis due to iron depleted erythropoiesis. This resulted in the low MCH and MCHC as reflected by the score. However UGI causes of anaemia had a pattern that was opposite to lower GI, with a lower Hb, higher HCT (hemo-concentrated) lower MCV, and high MCH.

The MCV in the multivariate model contributed in a negative manner. The MCV in the univariate analysis was lower in lower GI causes as compared to upper GI and systemic causes. However when entered in the multivariate models this relationship was reversed. This was due to the relative contribution of MCV to the total risk in the presence of the other blood indices (HCT, MCH and MCHC).

The profile of blood indices in systemic causes of anaemia is typical of anaemia chronic disease, MCV is higher than other causes, MCH is lower, and RDW is lower.

The clinical scoring tool:

Iron deficiency anaemia could occur due to chronic blood loss from upper or lower GI tract or systemic causes. It is also possible that a patient could have multiple causes of blood loss [60, 97-103, 105, 126]. In practice when a patient is referred for investigation of unexplained anaemia, once history and physical examination are obtained, an upper or lower GI tract

investigation or both is performed. Traditionally blood indices have no role in this decision.

This study combined both symptoms score and blood score to generate a risk score predicting the likelihood of anaemia caused by an upper, lower GI tract or systemic cause.

Two types of scoring tools where generated, a full model that incorporated all symptoms and blood indices and a reduced model by selecting influential factors only. Due to the large number of variables, rarity of some symptoms the error margin of the full model will be high. Although it had a high discriminatory power as confirmed by the area under the Receiver Operator Characteristic curve compared with the reduced model it would be difficult to apply in clinical practice. The reduced model selected fewer factors and it will be easier to apply in clinical practice.

The clinical tool (table 6.13) generates three scores (upper GI, lower GI, and systemic score). Each score reflects the risk of anaemia caused by the respective site. It is clear from table 6.16 that the scores were higher when a respective site was identified as a cause of anaemia. Even when patients had more than one site contributing to the anaemia the score of that respective site was higher than other scores. Patients who had an upper GI cause for their anaemia had an average score of 65 in the reduced model compared with a score of 17 for lower GI tract and 33 for a systemic cause. Patients

who had upper and colonic cause of anaemia had both respective average scores higher than systemic causes (mean reduced model scores of upper GI score 62, lower GI 54, systemic 31) (table 6.16, figure 6.10). Patients with GI cancers at the respective sites also had high respective scores.

As the score was a continuous scale a cut-off point needed to be determined to classify patients into high and lower risk groups. By doing so if a patient scored higher than the cut-off, it indicated investigation of that site as a matter of priority. This cut-off had to achieve a minimum of 80% sensitivity, i.e. 80% of the population with respective group pathology have to score above the chosen threshold of the respective risk score. The performance of the risk scores was compared to current guidelines. The UGI risk scores identified > 80% of patients with UGI causes of anaemia. In contrast < 40% of these patients met the DoH and BSG guidelines of urgent referral. However, the risk scores resulted in a significant increase in the number of patients needing to be investigated. All UGI cancer patients scored high on the UGI score and only 75% met the DoH and BSG guideline. This was reproduced for lower GI pathology and cancers, except for a lower and similar referral rate between the scores and guidelines.

The scores had a better performance in detecting UGI causes due to the ability to take into account the haemoglobin value at all levels below normal in contrast the DoH 11g/dl for men and 10g/dl for women thresholds. It also

performed better than the BSG guidelines due to the ability to take into consideration the different levels of MCV and other blood indices effect on risk. The resultant increase in referral is explained by the fact that majority of referred population had an UGI cause of anaemia and that upper GI causes had presented with higher MCV and milder anaemia.

In the case of lower GI causes and cancers, although the guidelines had a reasonable sensitivity (majority of patients had a low MCV and lower Hb), they had lower specificity. The scores identified more patients with pathology than the guidelines without increasing the referral rate. This higher specificity and sensitivity is due to accounting for the effect of blood indices and symptoms in prediction of site of blood loss. (Table 6.9 and 6.14)

In summary incorporating presenting symptoms and blood indices at time of referral generated a risk score predicting the likely site of blood loss. The scoring tool is able to differentiate patients with multiple causes of blood loss. Current guidelines will identify 75% of upper GI cancers, and 71% of lower GI cancers, but will miss more than 45 % of other causes of anaemia. The scoring tool will identify more patients with cancers and other pathology causing anaemia as high risk than current guidelines.

Chapter 7

Discussion and Conclusion

Colorectal and upper GI cancers are among the leading causes of cancer related death in the UK. Survival in the UK is yet to improve to come into line with survival from cancer in Europe. In addition to screening, the DoH has focused on improving the journey of patients at high risk of having cancer from referral to diagnosis, in an attempt to detect cancer at an early stage. The effectiveness of improving cancer survival has been achieved in colorectal cancer by mode of screening [127-129]. However, no advantage has been identified by introducing screening for upper GI cancer in the UK, which increases the emphasis for a need to improve detection of upper GI cancer in symptomatic patients.

IDA is a common denominator for high risk criteria for urgent referral of colorectal cancer and upper GI cancer. In 2000 the BSG introduced its guidance on investigating patients with IDA, which aim to streamline patient's investigations and ensure that the upper and lower GI tract are examined.

This thesis aimed to identify profiles of blood indices and symptoms that could aid in development of a streamlining scoring tool to aid investigation of anaemic patients.

Blood indices patterns of cancer

GI malignancies can present with anaemia secondary to overt or occult blood in the GI tract. This study investigated the blood indices profile in a consecutive cohort of common GI malignancies and a cohort from primary care.

Focused analysis of the anaemic profiles of oesophageal, gastric and proximal colon cancers (PCC) was undertaken. These cancers are representative of sites of the GI tract that commonly present with anaemia. Patients with distal cancer were not included in this study as they do not commonly present with anaemia [11, 90]. However when distal colonic cancer does presents with anaemia it is similar to PCC in profile[90].

In this cohort a significant number of PCC and gastric cancers are anaemic at presentation (PCC 75%, gastric cancers 67%). In contrast less than a third of oesophageal cancers (27%) presented with anaemia.

Sub analysis of anaemic cancer patients demonstrated a significant difference in anaemia profile of cancer groups. PCC had a lower MCV, MCH, MCHC and a higher RDW than upper GI cancers. These profiles are indicative of iron deficient state[48, 92]. PCC when compared to distal cancers commonly presents with IDA [11, 12, 90, 130, 131]. The profile of blood indices of colorectal cancers was studied in detail by Sadahiro *et al.* [90]. They demonstrated a tendency for PCC at later stages of cancer and larger

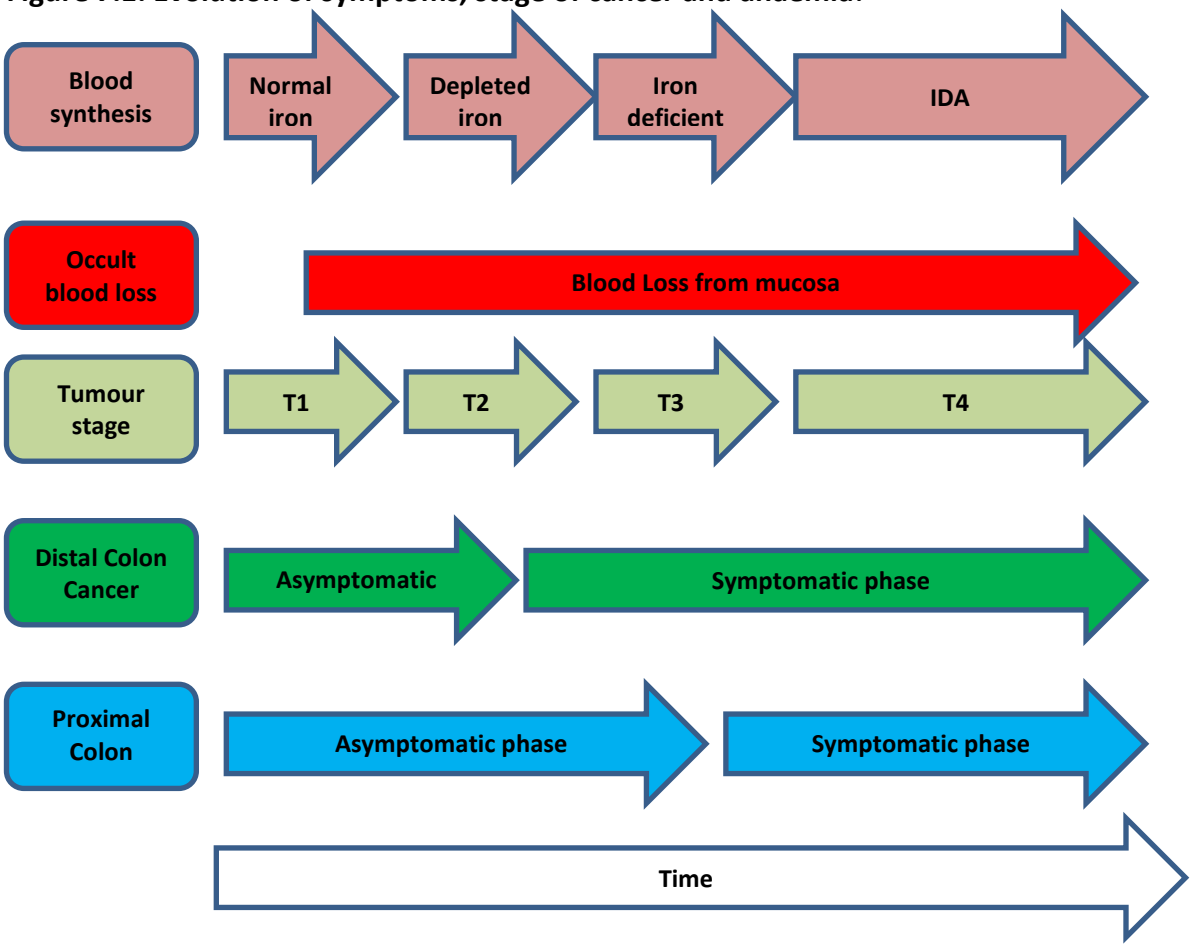
tumours to present with lower Hb and lower iron levels. No study has looked at the difference in the profile of blood indices between upper and lower GI tract in depth. The difference in the MCV, MCH, MCHC and RDW between upper and lower GI cancers is attributed to the level of iron deficiency. Studies that measured blood loss from the GI tract demonstrated a tendency of colonic causes to have detachable blood loss in whole gut lavage [93, 94]. It was found that in patients who had an obvious condition in the upper GI tract that is commonly seen in patients presenting with IDA, whole gut lavage was negative[93]. The investigators suggested that the blood loss from these lesions is either intermittent or the pathologies were coincidental. The former is likely as anaemia resolves once the conditions are treated. High bioavailability of heme iron [92] could explain the slower progression of upper GI blood loss to IDA, as a high proportion of lost iron from the GI tract is reabsorbed in the duodenum.

RDW is a reliable early index to detect IDA[132]. It has a high sensitivity and specificity for PCC [89]. In our cohort RDW had a tendency to increase with PCC as compared to upper GI cancers. The value of RDW is higher when Hb is normal [89], as it detects iron deficient state before anaemia ensues. This is represented in our data with the higher RDW in PCC compared with upper GI cancers, which reinforces the earlier onset of iron deficiency in PCC than on upper GI cancer.

Chronic blood loss from the GI tract results in a gradual depletion of iron stores, which will eventually result in anaemia. This process has phases. Reduction in size and haemoglobin content of RBCs occurs in iron deficient erythropoiesis before anaemia occurs. This early phase of iron deficiency will produce different populations of red blood cells, which is seen in blood films as poikilocytosis and that could be measured in FBC analysis as a high RDW. Cancer has two phases, an asymptomatic and a symptomatic phase. Along the same time line tumours continue to grow causing an advancement of stage and increase in GI blood loss. Using symptoms to detect cancer successfully at an early stage relies on an overlap period of early stage of cancer with early symptom phase (Figure 7.1). The longer this period is the higher the success rate of cancer detection, provided that the patients and health professionals have high awareness and vigilance.

In the GI tract where luminal space is relatively small (oesophagus, distal colon), the growth of a tumour will result in the presence of symptoms earlier compared with more capacious viscera (stomach, proximal colon). This explains the higher predictability of distal colonic symptoms for distal colon cancer and dysphagia for oesophagus. Hence blood loss from cancers in the proximal colon and stomach gains more relevance as symptoms, when they emerge, will be related to a later stage of cancer (Figure 7.1).

Figure 7.1: Evolution of symptoms, stage of cancer and anaemia.



The DoH and BSG referral guidelines anaemia thresholds were met in only 22% and 25% of the GI cancer cohort respectively. PCC had a higher proportion of cancers meeting the DoH and BSG referral thresholds (39%, 49% respectively) compared with gastric (16%, 19% respectively) and oesophageal cancers (7%, 7% respectively). Due to the higher threshold of referral of DoH and BSG referral guidelines, a drop from of 57% detection rate for GI cancers to 22% and 25% respectively was observed. By lowering the referral thresholds to include any patients with unexplained anaemia

regardless of MCV needing urgent assessment, a significantly higher proportion of cancers will be identified. However this is will increase the demand.

The first recommendation of this thesis thus is to lower the threshold of referral to achieve a higher sensitivity for cancer detection. But to improve specificity a further adjunct to that criterion is needed.

Symptoms of GI conditions and the identified different profiles of anaemia of GI cancers (Low MCV MCH, MCHC, higher RDW in PCC compared with upper GI cancer) provides a potential for a differentiating tool to aid in identifying patients who have significant GI causes of anaemia.

Diagnosis, symptoms and blood profiles of cohort investigated for unexplained of anaemia.

In the second stage of this research a cohort of patients with unexplained anaemia underwent an upper and lower GI investigation for causes of anaemia with a cause established in 95% of patients. 6 patients had iron deficiency responding to iron and resolved completely with no further pathology identified at one year follow up. High compliance with invasive investigations was observed, although compliance with FOB testing was poor.

This study confirmed that upper GI causes of occult blood loss were the commonest (40%), followed by systemic (30%) and lower GI causes (14%). Cancer incidence was highest in the lower GI tract with 65% of the patients with a lower GI cause of anaemia having colon cancer followed by patients who had dual upper and lower GI patients with 55% having colon cancer in addition to a benign upper GI cause of anaemia.

It was evident that compliance with national guidelines was poor as many patients with alarm symptoms and anaemia were not referred urgently. However 28% of dyspeptic patients who had anaemia were referred urgently and only 22% of patient with dysphagia were referred urgently.

The commonest upper GI symptoms of heart burn and dyspepsia had an associated significant cause of anaemia in 48% and 50% of patients respectively.

The incidence of heart burn and reflux has been reported to be 10% to 48% in the general population [30]. Dysphagia was reported in 9(7%) of the studied cohort. None of the upper GI symptoms had a significant difference in their distribution with respect to cause of anaemia, type of cancer or route of referral.

Dyspepsia is non specific to organic conditions of the upper GI tract[107]. However, when detailed scoring of symptom has been performed, it was

able to identify patients at high risk of having significant pathology in the upper GI tract[108].

The yield of cancer diagnosis from symptom referrals for patients with alarm symptoms of upper GI tract has been low, with incidence ranging from 4% to 15% [74, 109].

The value of these symptoms in our anaemic patients was not confirmed in univariate or multivariate analysis. However when mutually exclusive symptoms were removed by stepwise regression analysis, dysphagia approached significance in male patients. It was thus selected in the streamlining tool.

Previous studies have included high risk symptoms such as dysphagia and weight loss as individual factors or in scoring systems to identify significant upper GI disease and cancer with success, with an odds ratios of 2 for upper GI disease and 6 for cancer [31, 74, 110].

Change in bowel habit to loose motion or alternating loose motion and constipation was the commonest lower GI symptom reported. None of the lower GI symptoms had a significant relationship with a site of cause of anaemia except for constipation which was higher in patients with upper GI cancer (22%).

Loose motion and blood in the stool in the absence of perianal symptoms are high risk factor for significant lower GI disease with high predictive value for

cancer, colitis and large polyps [18, 27, 111, 112]. However their association with PCC is poor. Loose motion has been included in a risk score by Fijten *et al* to predict colorectal cancer [12]. However Majumdar *et al* demonstrated 1.96 odds ratio of distal cancer when cluster symptoms (included loose motions) existed [11]. Even in the presence of anaemia loose motions does not help predict PCC.

Stepwise regression analysis of lower GI symptoms demonstrated a reverse trend relationship between loose motions and significant lower GI pathology. This is explained by the fact that only 26 % of the cohort had a colonic condition that is commonly associated with loose motion. Loose motion was also prevalent in patients with upper GI disease (58%) and the majority of anaemic patients had upper GI disease. The above two reason rendered loose motion less specific to colonic conditions. This explains the reverse relationship.

Weight loss was reported in 32 (25%). The majority of these patients had a significant upper GI cause of anaemia. Only 19% of the cancer patients reported weight loss.

Blood profiles showed patterns that were correlating with causes of anaemia, with cancer patients having significantly lower haemoglobin and other blood indices compared with the non-cancer patients. Upper GI causes had a tendency to have a higher MCV, MCH and lower RDW compared with

lower GI causes. This is explained by the longer silent phase of lower GI cancers and the potential of re absorption of heme from the upper GI tract slowing the progression of iron deficiency.

Iron studies, as well as B12 and folate, did not show significant differences between site causes of anaemia. However, cancer patients did show a low ferritin level compared with non-cancer patients. This was even more pronounced in colonic cancers compared with upper GI cancers.

Results of logistic regression and stepwise regression analysis demonstrated a pattern of blood profiles that correspond to site of cause of anaemia. Systemic causes of anaemia had a higher MCV, and MCHC with a lower RDW, MCH, and HCT. This reflects the common mechanism of non-GI causes of anaemia in this population [49, 113, 114]. Erythropoiesis is deprived of iron as it is sequestrated in chronic inflammation response[49]. It is common that these patients present with normocytic (normal MCV), normochromic (normal MCHC)[48, 115].

The relatively normal RDW is likely due the slow development of anaemia in this patients and chronicity of the condition which results in a homogenous population[116]. As there is anaemia, the HCT and MCH decrease.

When assessing the pattern from GI causes of anaemia; it is evident that there is a pattern differentiating upper vs. lower GI causes.

In univariate analysis colonic causes of anaemia had a lower MCV, MCH, MCHC and a higher RDW compared with upper GI causes. This is similar to the demonstrated pattern in this study of GI cancer anaemic profiles. The regression analysis confirms the trend of higher MCH, HCT and higher serum iron in upper GI causes, and lower MCHC, MCH and HCT in lower GI causes. The regression models using blood indices demonstrated a good discriminatory power to sites of cause of anaemia independently and in combination with symptoms.

A prediction model was designed using the interaction between symptoms and the identified trends of blood indices with the site of cause of anaemia. Both the symptom based scoring models were effective in discriminating lower GI causes of anaemia (AUC 0.86) better than models for upper GI(AUC 0.72) and systemic causes(AUC 0.69).

Patients with upper GI cancer scored high on upper GI prediction model compared with other patients. Likewise, lower GI cancer scored high on the lower GI scoring tool compared with other patients.

The streamlining tool in clinical setting

Two prediction models were calculated for each site, a full symptom and blood comprehensive model and a reduced model. In order to allow for better implementation of the scoring tool in a clinical setting a simple and

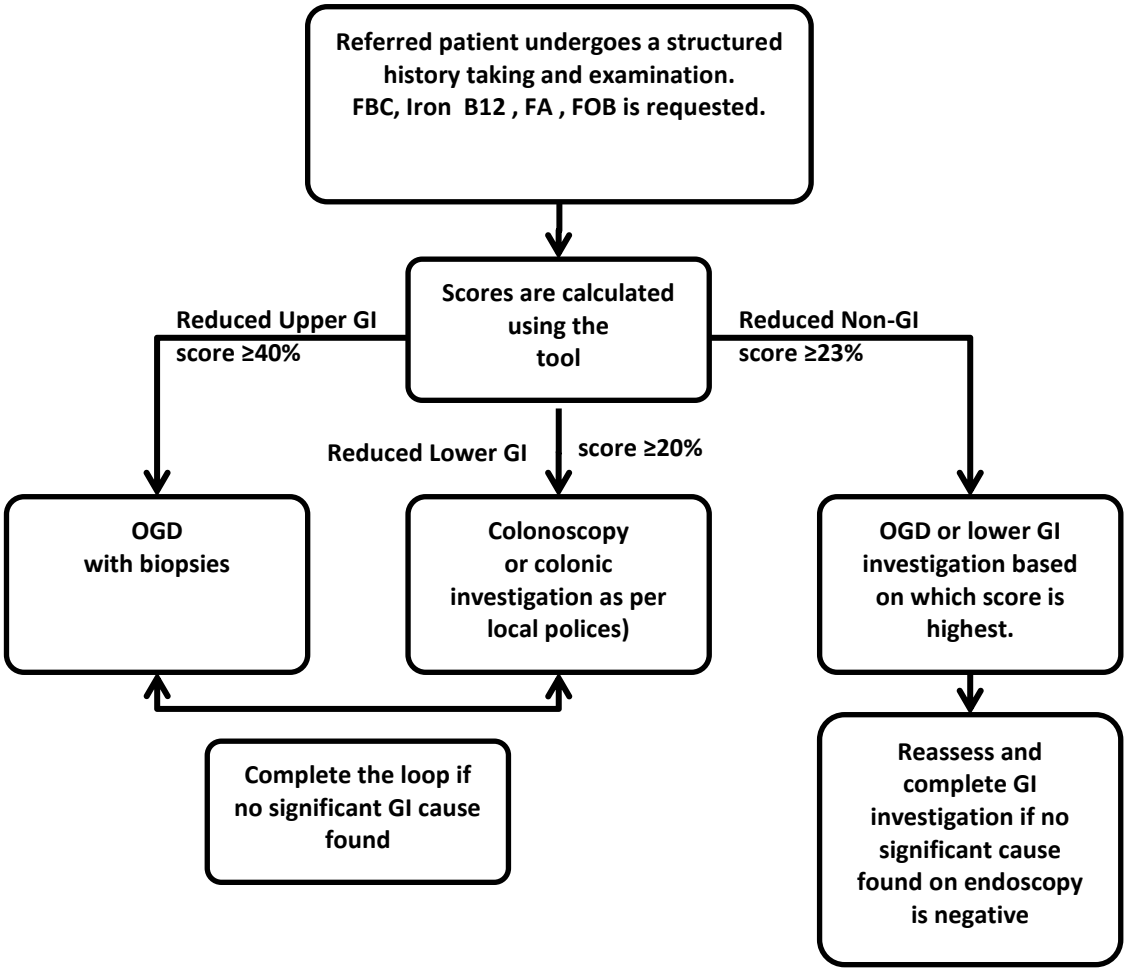
practicable tool is needed. The full model involves entering all factors in a large complicated equation. Hence it was not suitable for clinical settings. Stepwise regression analysis provided a systematic approach in selecting factors for the reduced model.

The reduced model had a higher sensitivity and specificity to detecting causes of anaemia compared with the current guidelines. It was also effective in predicting the site of cause of anaemia. Although the models had a higher sensitivity to cancer compared with the guidelines this did not reach statistical significance.

Recently there has been a rise in the use of scoring modalities in clinical settings. Such scoring modalities could provide a risk estimation for surgery as is in the POSSUM score [81, 119], mortality risk of critically ill patients as in APACHE II[122, 123, 133], prioritisation of patients based on severity of symptoms as is in the Oxford Hip Score [134-137], or risk of cancer based on colorectal symptoms like that achieved by the Selva score[111]. The success of these models is dependent on the efficacy of the score and their practicality and ease of use.

A scoring tool that would help streamline and identify patients at risk of having a significant cause of anaemia has been developed. It can be used in conjunction with current BSG guidance to help identify patients who have dual pathology and hence would need a bidirectional endoscopy (figure7.2).

Figure 7.2: Proposed clinical pathway for streamlining investigation of patients with anaemia



55% of patients who had dual pathologies of both upper GI and colonic causes of anaemia had colon cancer as the lower GI cause. Had the BSG guidelines been adhered to, then an OGD would have been organised. As a result of that, a significant upper GI pathology would have been identified and ultimately identification of the colon cancer would have been dependant on anaemia not resolving after trial of treatment or development of symptoms pertaining to the lower GI tract. Both possibilities would result in

delay in diagnosis and potentially result in advancing the stage of cancer. The scoring tool would identify these patients requiring bidirectional endoscopy and eradicate delay in detecting the colon cancers.

The current referral guidelines for suspected cancer have not as yet achieved an improvement in stage of upper or lower GI cancers detected. There has been however a reduction in emergency admission rates in colorectal cancers [138]. This success is multi factorial, but there is evidence that the reduction in delays in diagnosis of symptomatic colorectal cancers is contributing to this. Improvement in upper GI cancers emergency admission is yet to be demonstrated.

In this study only 4 upper GI cancers were identified. Hence it would require a larger study to assess the effect of the tool on the stage of upper GI cancer. Prior to the introduction of referral guidelines none of the PCC presented with anaemia and early stage of cancer at our hospital (table 7.1).

There was a significant delay in completing colonic investigation following upper GI investigation (Chapter 1, Table 1.5). Furthermore, haemoglobin had to drop below 100 g/l in females and 110 g/l in males before an urgent investigation was triggered.

In this cohort, 23% of PCC were Duke's A stage. This stage migration was statistically significant (chi-square, *p=0.02)* and achieved a post hoc power of

76%. This indicates a potential of the implemented protocol to improve stage of cancer at diagnosis.

Table 7.1: Duke stage of anaemic proximal colon across two reference periods.

Dukes Stage	PCC in Cohort(2003-2004)	Anaemic PCC between 1998-2001
A	3(23%)	0
B	3(23%)	17(44%)
C	5(39%)	15(38%)
D	2(15%)	7(18%)

Lowering the threshold of anaemia to trigger an urgent referral earlier and use of the scoring tool would help identify patients at risk of having a serious cause of anaemia in the GI tract. It will also help identify patients with potential significant dual pathologies.

In this study a dedicated anaemia clinic provided rapid assessment of patients referred with unexplained IDA. It has a structured interview format with a standardised investigation protocol. The clinic was doctor led, however it has the potential to be run by a nurse practitioner trained to apply the protocol. At the end of the study period the accompanying nurse practitioner was capable of applying the pathway safely and effectively.

It is proposed that the patient is interviewed using the structured scoring tool and blood profile results are obtained (table 6.13). He or she could be

directed to the investigation pathway of the score that is above the threshold (figure7.2). If a diagnosis is not established then reassessment of the GI tract needs to be considered and perhaps repeat GI investigations with a different modality.

Patients who score high on the systemic score and below the threshold in the other two scores should have the investigation of the highest GI score (figure 7.2). If that is clear then complete the loop of GI investigation. However on validation of the tool on a larger population, should the systemic score be so sensitive and specific, patient with low GI scores and high systemic score could avoid an un-necessary investigation.

One of the limitations of this study is a lack of complete assessment of the small bowel in all patients. Particularly in patients labelled as having systemic disease. Although requested, small bowel assessment was not completed except in patients who had high suspicion of small bowel pathology. Interestingly, after a 1 year follow up none of the patient developed small bowel pathology. This however does not exclude the potential of missing celiac disease, or small bowel disease.

Celiac disease was diagnosed in 7 studies out of the 18 reviewed (chapter 1). The incidence ranged from 2% to 11% (table 1.9). In 2 studies other small bowel pathologies were identified [100, 102].

The proposed streamlining pathway in addition to its compliance with recommended BSG guidelines, would also achieve a diagnosis of site specific pathology more rapidly as the loop is started with the highest yield test. It also allows for quantifying the risk of dual pathology allowing for direct booking of patients to bidirectional endoscopy, which in turn saves times and resources.

Conclusion

A scoring tool has been developed which could be applied in the clinic or incorporated into computer-based decision support software.

Validation of the tools accuracy and efficacy and further refinement is essential on a larger population.

IT is recognised however that there are limitations in the studies which have been conducted.

There are multiple factors that have been evaluated and the current sample size and the high number of symptoms does not allow for reliable statistical analysis. This work has been used as a pilot study to identify potential factors that could aid in the development of the scoring tool and set the foundation for a validation study.

Small bowel investigation was selective, So there is a risk of missing small bowel disease. That is also a risk with current guidelines for conditions other than coeliac disease.

We propose validation of the tool on a larger cohort. The primary outcome is to validate the accuracy of the scoring tool to achieve a correct diagnosis in 90% of the patients. That cohort can be used to further refine the score and investigate the utility of adding further symptoms to the score.

A nurse led clinic could also be explored and feasibility and safety could be confirmed.

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Appendixes

Appendix 1: Literature review of studies investigation patients with iron deficiency anaemia

Reference	*N*	*Upper GI*	*Colorectal Cause*	*Dual*	*Non GI*	*Note*
Annibale et al[57]	*71(85%)*	*Gastric Cancer 2* *Peptic ulcers 7* *Hiatus Hernia with erosion 5* *Atrophic gastritis 19* *Celiac 4* *H pylori 13*	*Colon Cancer 10* *Vascular Ectasia 3* *Polyps 2* *Crohn's 1*	*8%*		*Non bleeding causes seen in younger patients*
Gordon et al [66]	*170*	*70(41%)* *Peptic ulcer 15%* *Oesophagitis 8%* *Gastritis 75* *Gastrectomy 6%* *Celiac disease 3%*	*30(18%)* *Colon cancer 9%* *UC 4%* *AVM 3%*		*70(41%)*	

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Cook et al[39]	***100***	***60(60%)*** ***Oesophagitis 14*** ***Erosions 14*** ***Ulcer 8*** ***Oesophageal cancer 1*** ***Gastric cancer 5*** ***HH > 10cm 7*** ***Varices 3*** ***Angiodysplasia 5*** ***Gastric surgery 10***	***23(23%)*** ***Cancer 14*** ***Polyps 6*** ***Vascular ectasia2*** ***Ulcerative Colitis 1*** ***Crohn's 2***		***12(14%)***	
Rockey et al[64]	***100***	***37(37%)*** ***Ulcer 19*** ***Oesophagitis 6*** ***Gastritis 6*** ***Vascular ectasia 3***	***26 (26%)*** ***Prox Colon Cancer 8*** ***Distal Colon Cancer 3*** ***Angiodysplasia 5*** ***IBD 2***	***1%***	***38%***	

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		Gastric cancer 1 *Polyp 1* *Portal hypertensive gastropathy 1*	*Caecal ulcer 2* *Polyp 5* *Parasitic infestation 1*			
Zuckerman et al[40]	*100*	*36(36%)* *Oesophagitis 6* *Gastric Ulcer 6* *Erosion 12* *Duodenal Ulcers 1* *Duodenal erosioin2* *Vascular ectasia 8* *Varices 2* *Polyp 1* *Gastric cancer 1*	*26(26%)* *Polyps 14* *Colon cancer 6* *Vascular ectasia 5* *Ulcers 2*	*9(9%)*	*47(47%)*	
McIntyre et al [37]	*111*	*45(39%)* *Gastric ulcer 13*	*18(16%)* *Polyp 8*	*10(9%)*	*31%*	*OGD flexi and barium enema*

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		Duodenal ulcer 10 *Gastric cancer 8* *Oesophagitis 15* *Erosive Gastritis 7* *Celiac disease 3* *Gastrectomy 2* *Other ? NSAID 2*	*Prox colon cancer 4* *Distal colon cancer 1* *Ulcerative Colitis 2* *Vascular ectasia 1* *Other 3*			*Only 93 patients completed full upper and lower GI investigation.*
Hardwick et al[41]	*89*	*53(60%)* *Oesophagitis 26* *Barrett's ulcer 1* *Oesophageal cancer 2* *Gastric Cancer 7* *Peptic Ulcer 10* *Lymphoma 2* *Celiac disease 2* *Jejunal cancer2* *Ampullary cancer 1*	*50(58%)* *Prox colon cancer 26* *Distal colon cancer 7* *IBD 9* *Colonic polyps 8* *Angiodysplasia 2* *Ileal carcinoid 1*	*26(29%)*	*9*	

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Kepczyk et al [65]	*70*	*39(56%)* *Gastric Erosions 11* *Oesophagitis 10* *Watermelon stomach 4* *Celiac 4* *Gastric Ca 3* *Gastric Ulcer 3* *Duodenal Ulcer 3* *Polyps 2* *Lymphoma 1* *Oesophageal cancer 1* *Crohn's disease 1*	*21(30%)* *Prox colon cancer 2* *Distal colon cancer 2* *Polyp 7* *Vascular ectasia 6* *Haemorrhoids 4* *IBD 1*	*12(17%)*	*5 (7%)normal*	*Piles 60ml a day >3/weeks fro 6 month*
Landy et al[59]	*478*	*63(13.2%)* *Cancer 10* *Oesophagitis 4* *Stricture 1*	*62(13%)* *Cancer 24* *Polyp 18* *Vascular ectasia 11*	*7(1.5%)*		*Retrospective analysis of prospective collected data.*

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		Barrets 20 *Ulcers 17* *Vascular ectasia 12*	*IBD 9*			*Only reported predefined causes of IDA. Gastritis, duodenitis was not reported even if it was the only finding*
Nahon et al [60]	*117*	*54(46%)* *Gastritis 17* *Oesophagitis 9* *Cancer 7* *PUD 9* *Gastric polyp 6* *Vascular ectasia 3*	*31(26.5%)* *Cancer 14* *Polyp 10* *Vascular ectasia 5*	*4%*		*Women only.*
Urquhart et al[61]	*6538*	*2184(33%)* *Cancer 22*	*1505(23%)* *Cancer 116*			*Retrospective analysis of*

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		Vascular ectasia 231 *Ulcers 377* *Barret's 252* *Stricture 241*	*Vascular ectasia 251* *Polyp 409*			*prospectively collected data. 20.9% of the population was under 50years old only 5%<40 Other findings not listed(16% upper GI , 11% lower GI)*
Capurso et al [78]	*98*	*20(20%)* *Ulcer 9* *Hiatus hernia with Cameron ulcers 7* *Gastric Cancer 5* *Atrophic gastritis 14* *H pylori 15* *Coeliac disease 11*	*27(27.5%)* *Colon cancer 13* *Polyp 4* *Vascular ectasia 4* *Severe Diverticular disease with FOB+ 5* *IBD 1*	*8(8%)*		

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		Gastric surgery 5				
Park et al[104]	***749***	***Oesophagitis 1*** ***Gastritis 16*** ***Peptic Ulcers 71*** ***Polyp 1*** ***Gastric cancer 14***	***Colon cancer 25*** ***Piles 25*** ***Tuberculosis 8*** ***IBD 9*** ***Vascular ectasia 3*** ***Polyp 21***			
Bampton et al [99]	***80***	***Oesophagitis 14*** ***Peptic Ulcers 8*** ***Gastric Polyp 4*** ***Gastritis 2*** ***Portal hypertensive gastropathy 2*** ***Gastric cancer 1*** ***Vascular ectasia 1*** ***Duodenal polyp 2***	***Colon cancer 7*** ***Polyps 5*** ***Colitis 1*** ***Vascular ectasia 1***			

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		Hiatus hernia >10cm 2 *Post-Gastrectomy 3*				
Joosten et al [63]	*96*	*Oesophagitis 12* *Gastritis 17* *Gastric ulcer 5* *Duodenal ulcer 7* *Vascular ectasia 6* *Polyp 4* *Gastric cancer 2*	*Polyp 10* *Vascular ectasia 6* *Colitis 1* *Colonic cancer 13* *Piles 1*			*Elderly >70years old*
Sari [103]	*95*	*Gastritis 16* *Duodenal ulcers 15* *Gastric ulcers 8* *Gastric cancer 7* *Celiac disease 2* *Oesophagitis 7*	*Colon cancer 5* *Piles 3* *Polyps 1* *Colitis 1*		*Normal 30*	*Age > 50years*
Coban[76]	*96*	*Duodenal ulcer 14*	*Colon cancer 8*	*I dual pathology*		

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		Gastritis 12 ***Oesophagitis 11*** ***Gastric ulcer 11*** ***Gastric cancer 6*** ***Polyp 3*** ***Oesophageal cancer 1***	***Piles 6*** ***Polyp 3*** ***Diverticular disease 3*** ***Vascular ectasia 2*** ***Colitis 2***			
Niv et al[102]	***48***	***Oesophagitis 2*** ***Hiatus hernia with erosions 2*** ***Gastritis 9*** ***Duodenitis 1*** ***Duodenal ulcer 1*** ***Gastric cancer 2*** ***Small bowel cancer 1***	***Polyps 3*** ***Colon cancer 11*** ***Vascular ectasia 3***	***3 dual pathology***		

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Appendix 2: Anaemia symptom proforma

Anaemia Investigation Proforma

NHS
MID CHESHIRE HOSPITALS

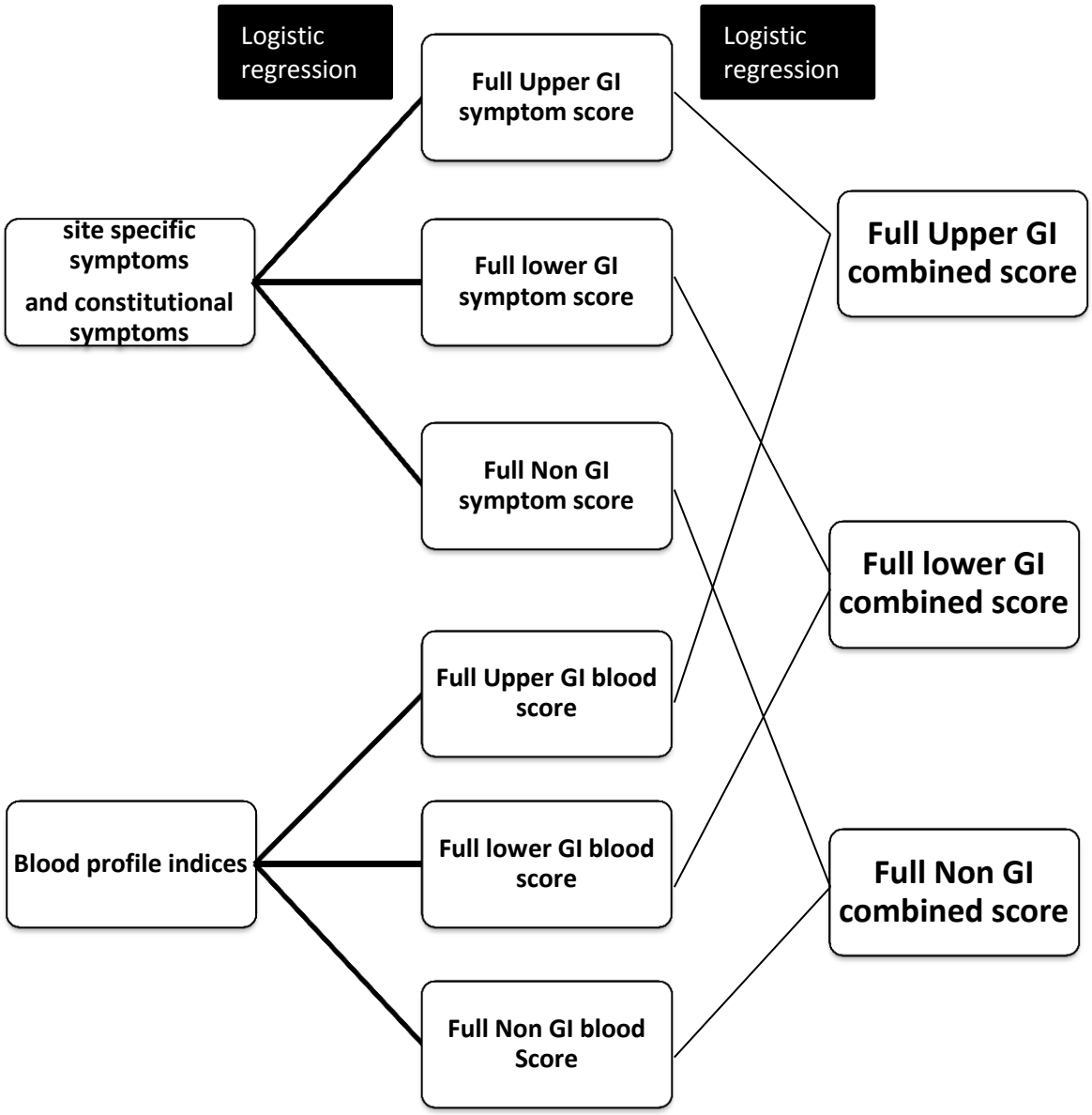
Patients Sticker

Date:
Consultant:
Entered By:

Patient Symptoms	Tick if yes	
Male or Female < 45 Years of Age		
Male or Female >45 Years of Age		
Pre menopausal Women		
Heavy period		
Upper GI symptoms		
Heart Burn or Reflux		
Dyspepsia		
Upper abdominal pain		
Nausea		
Vomiting		
Dysphagia		
Previous History of Gastric Surgery		
Melena or Hematemesis		
Small Bowel Surgery		
Blood in stool		
Change in bowel habits to loose motion		
Slime in stool		
Increased frequency of stool		
Constipation		
Central or lower abdominal pain		
History of Inflammatory bowel disease		
History of Polyps		
Family history of colon cancer		
Right iliac fossa (RIF) pain		
Systemic Symptoms		
Weight Loss		
Loss of appetite		
Brittle or abnormal nails		
Sore tongue		
Night Sweats		
Pruritus		
Joint pain		
PMH of Rheumatoid Arthritis		
PMH of Chronic Renal Failure		
On NSAIDS or Aspirin		
On Steroids		
Other medication		

Examination of Patient					
Right Iliac Fossa Mass or fullness.					
Tumour on Per-rectal Examination.					
Investigation FBC, Iron, Ferritin, FOBx3, Urinalysis, B12, Folate					
OGD	*Colonoscopy*	*Flexi sigi*	*Barium enema*	*CT*	

Appendix 3: Multistep approach in development of the full scoring tool.



Appendix 4: Multistep approach in development of the reduced scoring tool.