

# Impact of small bowel capsule endoscopy in iron deficiency anemia: influence of patient's age on diagnostic yield

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**ABSTRACT – Background** – Iron deficiency anemia remains one of the main indications to perform small bowel capsule endoscopy. Literature suggests that diagnostic yield is influenced by patient's age but with conflicting results regarding age cutoff. **Objective** – We aimed to clarify the differences in diagnostic yield and incidence of specific findings according to age. **Methods** – Retrospective single-center study including 118 patients performing small bowel capsule endoscopy in the study of iron deficiency anemia. Videos were reviewed and small bowel findings that may account for anemia were reported. Incomplete examinations were excluded. Findings were compared between patients  $\leq 60$  and  $>60$  years. **Results** – Patients had a mean age of 58 years old (SD  $\pm 17.9$ ) with 69.5% females (n=82). The overall diagnostic yield was 49% (58/118), being higher among patients  $>60$  years (36/60, diagnostic yield 60%) than those  $\leq 60$  years (20/58, diagnostic yield 34%), ( $P < 0.01$ ). Angiectasias were more frequent in patients  $>60$  years (45% vs 9%,  $P < 0.01$ ). Patients  $\leq 60$  years presented more frequently significant inflammation (Lewis score  $> 135$  in 10.3% vs 1.7%,  $P < 0.05$ ) and other non-vascular lesions (24% vs 10%,  $P = 0.04$ ). **Conclusion** – In our cohort small bowel capsule endoscopy diagnosed clinically relevant findings in the setting of iron deficiency anemia in almost half the patients. Diagnostic yield was higher in patients older than 60 years (60%), with vascular lesions being more frequent in this age group. Despite the lower diagnostic yield in patients  $\leq 60$  years, significant pathology was also found in this age group, mainly of inflammatory type.

**HEADINGS** – Anemia. Capsule endoscopy. Small intestine.

## INTRODUCTION

Iron deficiency anemia (IDA), the most frequent cause of anemia<sup>(1)</sup>, has a prevalence of 2%-7% in the general population and is particularly frequent in the elderly, with a prevalence of 10-12<sup>(2)</sup>. Since chronic occult gastrointestinal bleeding is the main cause for IDA, upper and lower gastrointestinal endoscopies are the first line diagnostic procedures<sup>(3)</sup>. However, about 30% of patients will have normal bidirectional endoscopy<sup>(4)</sup>, making small bowel endoscopy the next step in the diagnosis.

Capsule endoscopy has become an important aid in clinical practice, providing the diagnosis in many situations that were previously hard to identify. Occult gastrointestinal bleeding (OGIB) remains one of the main indications to perform small bowel capsule endoscopy (SBCE)<sup>(5)</sup>. In this setting, when compared with other small-bowel imaging techniques, SBCE has significantly higher diagnostic yield (DY) than small bowel follow-through, push enteroscopy, CT enteroclysis, CT angiography and MRI, and is comparable to double balloon enteroscopy<sup>(6-8)</sup>. In face of such evidence, current guidelines recommend capsule endoscopy as the first-line investigation of OGIB<sup>(9)</sup>.

In the setting of IDA, SBCE has a pooled diagnostic yield of 66.6%<sup>(10)</sup> influencing subsequent clinical management in 72%-75% of patients with positive SBCE<sup>(11)</sup>. The most frequent findings are

angioectasias but other vascular abnormalities, inflammatory lesions or small bowel tumors can also arise<sup>(10)</sup>.

Current literature suggests that diagnostic yield is influenced by patients' age but with conflicting results regarding the age cutoff<sup>(11-14)</sup>. Also, current evidence suggests that diagnostic findings on SBCE performed in the setting of IDA are influenced by patients' age<sup>(11-13)</sup>. We aimed to assess the diagnostic yield of SBCE in patients with IDA after negative upper endoscopy and colonoscopy, and to clarify the differences in DY and incidence of specific findings according to patients' age.

## METHODS

Retrospective study in a University affiliated Hospital Gastroenterology Department, highly experienced in SBCE. All videos of consecutive SBCE performed in the study of IDA between September 2012 and August 2015 were reviewed, and small-bowel findings that could account for IDA were considered relevant. Those findings included visible hemorrhage or hematic residues, angioectasias, erosions, ulcers, varices, polyp/tumor and significant villous atrophy in proximal small bowel. Patients with inflammatory lesions had their Lewis Score (LS) calculated and were categorized according to the defined and validated cut-offs in three groups – non-significant inflammation if  $LS < 135$ , mild inflammation if  $LS 135 - < 790$  and moderate to severe inflammation if  $LS \geq 790$ <sup>(15)</sup>.

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Anemia was defined as hemoglobin below 12g/dL for women and 13g/dL for men and iron deficiency was defined as ferritin <15ug/L for patients with negative inflammatory markers, and ferritin <50ug/L for those with elevated inflammatory markers<sup>(3)</sup>.

All patients had undergone upper and lower gastrointestinal endoscopy before SBCE. SBCE was performed with PillCam® SB2 or SB3 (Medtronic, Minneapolis, MN, USA) using the standard protocol for our unit – clear liquid diet the day before the procedure and a 12h night-fast; 30 minutes before capsule ingestion patients were given 100 mg of Simethicone (Aero-OM®, OM Pharma) and 1h after ingestion they returned to our unit for real time visualization; at this point, if the capsule remained in the stomach, the patient was given Domperidone (Motilium®, Janssen). If after prokinetic administration the capsule remained in the stomach, it was passed into the duodenum by upper gastrointestinal endoscopy<sup>(16,17)</sup>.

The complete video obtained in each SBCE was reviewed by two gastroenterologists with vast experience in capsule endoscopy using Rapid® Software, at 8-12 frames per second rate, using when needed FICE technology<sup>(18,19)</sup>.

We collected data on age, gender, capsule type (PillCam® SB2 or SB3), quality of bowel preparation, gastric and small bowel transit time and presence of relevant findings in segments other than small bowel. Incomplete SBCE and repeat examinations for the same patient were excluded. SBCE findings were compared between patients ≤60 and >60 years.

Statistical analysis was performed using SPSS v.21.0 and a two-tailed *P* value <0.05 was defined as indicating statistical significance. Categorical variables were presented as frequencies and percentages, and compared with the use of Fisher's exact test or chi-square test, as appropriate. Continuous variables were presented as means and standard deviations and compared with the use of Student's *t*-test.

This study was performed in compliance with ethical standards and all patients signed an informed consent form and consensual contraindications for SBCE procedure were respected as have been described elsewhere<sup>(20)</sup>.

## RESULTS

From September 2012 to August 2015 a total of 357 SBCE were performed, 127 in the study of obscure OGIB. Out of these 127 patients, only 118 were considered for the purpose of this study – five patients had positive stool blood test without anemia and other four capsules were incomplete.

Patients had a mean age of 58±17.9 years old (minimum 20, maximum 86 years old) with 69.5% females (n=82). At the time of SBCE mean hemoglobin was 9.9±1.4 g/dL. SBCE was performed with PillCam® SB3 in 64 (54.2%) patients. Preparation quality was considered good in the vast majority of patients (66.9%). Information regarding patients' usual medications and comorbidities are depicted in TABLE 1.

The overall DY was 49.0% (58/118). No differences were found for DY between PillCam® SB2 and SB3 (50% vs 45.3%, *P*>0.05) nor between patients with good small bowel preparation when compared with moderate or bad preparations (41.8% vs 58%, *P*>0.05).

The most frequently reported findings were angioectasias in 27.1% of SBCE. The frequencies of endoscopic findings are depicted in FIGURE 1.

First, second and third tercile findings were reported in 51%, 25% and 30% of SBCE, respectively, and mean small-bowel transit

TABLE 1. Patients usual medication and comorbidities.

Usual medication	Percentage (%)
Acetylsalicylic acid	23.7
Clopidogrel	0.8
Warfarin	12.7
Low weight molecular heparine	0.0
Comorbidities	
Chronic renal failure	15.3
Hypertension	64.4
Dyslipidemia	56.8
Diabetes	23.7
Chronic liver disease	5.1

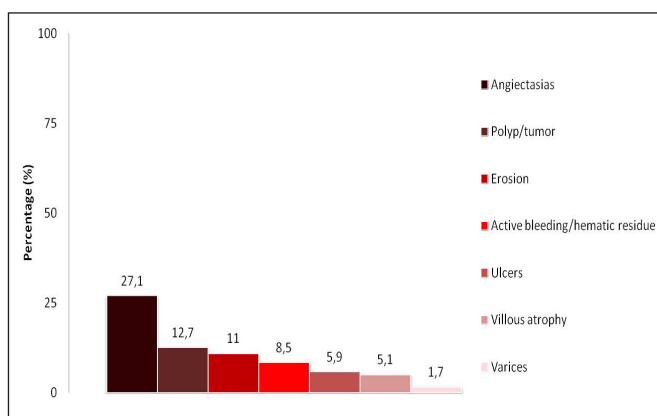


FIGURE 1. Frequency of relevant findings.

time was 274±105 minutes. No differences were found between SB2 and SB3 for first (42.6% vs 57.8%, *P*>0.05), second (25.9% vs 23.4%, *P*>0.05) and third tercile findings (33.3% vs 26.6%, *P*>0.05) or relevant findings detection (50% vs 45.3%, *P*>0.05). SB3 had a significantly higher detection of villous atrophy (0% vs 9.3%, *P*=0.03) but both capsules had comparable performances regarding other findings detection.

For patients with small-bowel inflammatory lesions, a LS>135 was reported in 5.9% of SBCE (n=6).

Relevant findings in segments other than the small bowel were reported in 20.3% of examinations, mostly in the stomach (17.8%) being erosions the most frequently reported finding in these segments (10.2%). Half of patients with extra-small bowel findings also had relevant small bowel findings.

DY was significantly higher for males (63.9% vs 40.2%, *P*<0.02). Also, patients with diagnostic SBCE were significantly older (62.4 vs 54.9 years, *P*=0.02) and had longer small bowel transit time (303.6 min vs 247.1 min, *P*<0.01). Even for PillCam®SB3, longer small bowel transit time is significantly associated with significant finding detection on SBCE (254 vs 312 min, *P*=0.026). DY was not influenced by antiplatelet/anticoagulant drugs or patients' co-morbidities (hypertension, dyslipidemia, diabetes mellitus, and chronic renal or hepatic disease).

The mean age of patients with angioectasias was 67±12.5 years, while the mean age of patients with non-diagnostic SBCE was 55±18.4 years. Patients with inflammatory lesions had a mean age of 45±15.7 years (TABLE 2).

TABLE 2. Mean age according to findings.

Finding	Patients mean age $\pm$ SD (years)
Angioectasia	67 $\pm$ 12.5
Polyp/tumor	60.9 $\pm$ 18.0
Erosion	56.1 $\pm$ 20.6
Active bleeding/hematic residue	60.6 $\pm$ 19.8
Ulcers	44.9 $\pm$ 16.0
Villous atrophy	66.3 $\pm$ 18.0
Varices	82.0 $\pm$ 5.7
No findings	55 $\pm$ 18.4
Lewis score >135	45 $\pm$ 15.7

Statistically significant differences between DY were found between patients  $\leq 60$  years (20/58, DY 34%) and those  $> 60$  years (36/60, DY 60%), ( $P < 0.01$ ). Angioectasias were more frequently found in patients  $> 60$  years (45% vs 9%,  $P < 0.01$ ). Also, dyslipidemia and hypertension were significantly more frequent in patients with angiectasia (51.2% vs 71.9%,  $P = 0.04$  and 58.1% vs 81.3%,  $P = 0.02$ , respectively). Patients  $\leq 60$  years presented more frequently significant inflammation (Lewis score  $> 135$  in 10.3% vs 1.7%,  $P < 0.05$ ) and non-vascular lesions (erosions, ulcers, villous atrophy and polyp/tumor) (24% vs 10%,  $P = 0.04$ ) (FIGURE 2). No differences were found in the detection of visible hemorrhage/hematic residues, ulcers, erosions, varices, polyp/tumor and villous atrophy between the two groups.

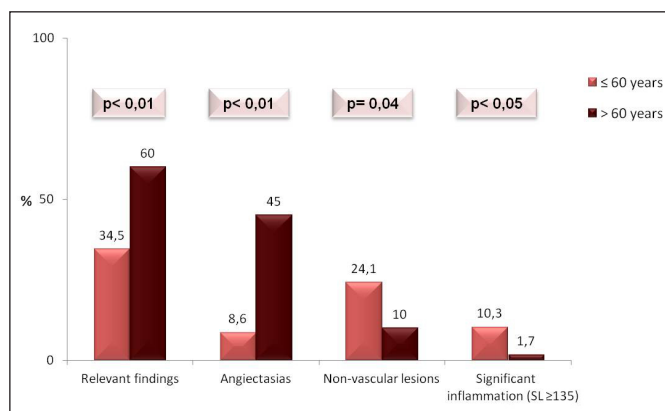


FIGURE 2. SBCE findings in IDA according to age.

## DISCUSSION

SBCE is currently widely accepted and recommended as first-line investigation tool in OGIB. Our study confirms that SBCE has a significant role in the study of IDA providing valuable diagnostic information in nearly half of patients. Other investigators have reported DY ranging from 27% to 77%<sup>(7,21)</sup> and Koulaouzidis et al. reported, in a recent systematic review, a pooled diagnostic yield of 66.6%<sup>(10)</sup>. We were also able to confirm that SBCE has greater diagnostic performance in older patients, with 60% DY for patients over 60 years. The latter finding strengthens previous evidence that older patients have higher DY, however different authors have presented different age cut-offs and, until now, no clear age delimitation was consistently established<sup>(11-14)</sup>. The higher

DY in patients over 60 years is usually attributed to their higher comorbidity and medication burden since previous studies reported that chronic liver disease, hematologic disease, chronic renal failure and anticoagulants intake influence diagnostic yield in older patients<sup>(11)</sup>. In our cohort such co-morbidities and therapies were not significantly associated with higher diagnostic yield which may indicate that other factors influence DY. Despite higher DY in older people, younger patients have significant pathology detected by SBCE in our cohort (34% DY) and other authors reported DY of 28%-50% in younger age groups<sup>(11,13,14)</sup>.

In our cohort, we found significantly higher DY in male gender. Some authors have reported that SBCE has low DY in pre-menopausal women with iron-deficiency anemia (13.7%)<sup>(22)</sup>. Since nearly a third of the women in our sample have  $\leq 45$  years, and we did not consider pre-menopausal status as an exclusion criterion for our study, this may account for the differences found between genders. What is more, the inclusion of young women irrespective of their pre-menopausal status may contribute to the lower diagnostic yield reported in younger patients.

We also found that patients with longer small bowel transit time (SBTT) have higher DY. Faster small bowel transit can eventually translate into a higher risk of missed lesions, particularly in the first tercile and several authors reported higher diagnostic yield with longer SBTT, including for SBCE performed in OGIB study<sup>(23)</sup>. PillCam<sup>®</sup> SB3 aims to overcome this limitation, by providing adaptable frame rate technology. However, in our cohort, even for PillCam<sup>®</sup> SB3, longer small bowel transit time is significantly associated with significant finding detection on SBCE.

In our cohort the most frequent finding were angiectasias in 27.1% of all patients, particularly in patients  $> 60$  years, who had angiectasia in 45% of cases, and in patients with hypertension and dyslipidemia. The former finding is in concordance with the literature that consistently associates higher angiectasia detection with older patients<sup>(11-14,24)</sup>. The pathogenesis of GI angiectasias is not fully understood, but some authors advocate that angiectasias should be regarded as degenerative lesions of aging, caused by chronic intermittent low-grade obstruction of veins, capillaries, and arterioles that supply the mucosa<sup>(25)</sup>. Also, previous authors have described hypercholesterolemia and hypertension as predictors of angiectasias, comorbidities increasingly more frequent with age and that may contribute to the higher prevalence of this finding in older patients<sup>(24)</sup>.

We found significant inflammation, assessed by a Lewis Score  $> 135$ , more frequently in younger patients, with a mean age of  $45 \pm 15.7$  years. For the majority of these patients Crohn's disease (CD) diagnosis was established during follow up, which is in agreement with the previously described high diagnostic accuracy and sensitivity of LS  $> 135$  for CD diagnosis<sup>(26)</sup>. This finding is also consistent with the widespread knowledge that inflammatory enteritis are more prevalent in younger populations and stresses the need to consider this diagnosis in patients presenting solely with IDA.

Even though all patients in our cohort had undergone upper and lower gastrointestinal endoscopy before SBCE, relevant findings in segments other than small bowel were reported in 20.3% of examinations, mostly in the stomach (17.8%). Other authors have reported extra-small bowel findings in 7% to 23%<sup>(27,28)</sup> of SBCE performed in the study of OGIB. Despite significant extra-small bowel findings detection rates, both Gilbert et al.<sup>(29)</sup> and Selby et al.<sup>(30)</sup> proved that a second look endoscopy before SBCE has low diagnostic yield, is not cost-effective, and is not recommended in

current guidelines<sup>(9)</sup>. Furthermore, in our sample, half of patients with extra-small bowel findings also had relevant small bowel findings reinforcing the need to assess this gastrointestinal segment in patients with previous unremarkable upper and lower gastrointestinal endoscopy.

Limitations of our study include its retrospective nature, making our sample widely heterogeneous in terms of therapeutical approach.

## CONCLUSION

In our cohort SBCE diagnosed relevant findings in the setting of IDA in almost half the patients. The DY was higher in patients older than 60 years (60%), with vascular lesions being more

frequent in this age group. Despite the lower DY in patients  $\leq 60$  years, significant pathology is also found in this age group, mainly of inflammatory type.

## Authors' contribution

Xavier S performed the literature search, collected and analyzed clinical data, designed the text structure and wrote the text. Magalhães J and Moreira MJ contributed to analysis and interpretation of data and made several critical corrections and revisions. Rosa B and Cotter J suggested the theme to be reviewed, and made the several critical corrections and revisions, including English editing, until the submitted version was achieved. All authors approved the final version of the article.

Xavier S, Magalhães J, Rosa B, Moreira MJ, Cotter J. Impacto da enteroscopia por cápsula na anemia ferropénica: influência da idade do doente no rendimento diagnóstico. *Arq Gastroenterol.* 2018;55(3):242-6.

**RESUMO – Contexto** – A anemia ferropénica constitui uma das principais indicações para realização de enteroscopia por cápsula. A literatura sugere que o rendimento diagnóstico é influenciado pela idade do doente, contudo, não é consensual o grupo etário para o qual o rendimento diagnóstico é maior. **Objetivo** – Clarificar as diferenças de rendimento diagnóstico e incidência de achados específicos de acordo com a idade. **Métodos** – Estudo retrospectivo unicêntrico. Incluídos 118 doentes que realizaram sistematicamente enteroscopia por cápsula no estudo de anemia ferropénica. Todos os vídeos foram revistos e foram reportados os achados no intestino delgado que pudessem ser a causa da anemia ferropénica. Excluídas enteroscopia por cápsula incompletas. Comparados os achados entre doentes com  $\leq 60$  e  $>60$  anos. **Resultados** – Doentes com idade média de 58 anos (SD  $\pm 17,9$ ), 69,5% do género feminino (n=82). O rendimento diagnóstico global foi de 49% (58/118), sendo superior em doentes  $>60$  anos (36/60, rendimento diagnóstico 60%) do que em doentes  $\leq 60$  anos (20/58, 34%). As angiectasias foram mais frequentemente reportadas em doentes  $>60$  anos (45% vs 9%,  $P < 0,01$ ). Nos doentes com  $\leq 60$  anos foi mais frequentemente reportada inflamação significativa (Score de Lewis  $>135$  em 10,3% vs 1,7%,  $P < 0,05$ ) e lesões não vasculares (24% vs 10%,  $P = 0,04$ ). **Conclusão** – Na nossa amostra, a enteroscopia por cápsula revelou-se importante no estudo da anemia ferropénica detectando achados relevantes em cerca de metade dos doentes. O rendimento diagnóstico foi maior em doentes com mais de 60 anos (60%), sendo as lesões vasculares mais frequentes neste grupo. Apesar do menor rendimento diagnóstico em indivíduos até aos 60 anos, foi detectada patologia relevante neste grupo, em especial do tipo inflamatório.

**DESCRITORES** – Anemia. Endoscopia por cápsula. Intestino delgado.

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