

Non-small bowel lesion detection at small bowel capsule endoscopy: A comprehensive literature review

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Abstract

Small bowel capsule endoscopy is a minimally-invasive endoscopic investigation that is often used in clinical practice to investigate overt or occult gastrointestinal (GI) bleeding among other clinical indications. International guidance recommends small bowel capsule endoscopy as a first-line investigation to detect abnormalities in the small bowel, when gastroscopy and colonoscopy fail to identify a cause of GI bleeding. It can diagnose with accuracy abnormalities in the small bowel. However, there has been increasing evidence indicating that small bowel capsule endoscopy may also detect lesions outside the small intestine that are within the reach of conventional endoscopy and have been probably missed during prior endoscopic investigations. Such lesions vary from vascular deformities to malignancy and their detection often alters patient management, leading to further endoscopic and/or surgical interventions. The current study attempts to review all available studies in the literature and summarise their relevant findings.

Key words: Obscure gastrointestinal bleeding; Small bowel capsule endoscopy; Non-small bowel lesions; Overt gastrointestinal bleeding; Occult gastrointestinal bleeding; Iron deficiency anaemia

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Core tip: Video capsule endoscopy can accurately diagnose small bowel pathology, but often also detects abnormalities in the upper and lower gastrointestinal tract within the reach of conventional endoscopy, that have probably been previously overlooked.

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INTRODUCTION

More than a decade ago, the emergence of novel modalities for the diagnosis and treatment of small bowel diseases revolutionised the landscape of gastrointestinal endoscopy. Small bowel capsule endoscopy (SBCE), a non-invasive method of direct visualisation of the small intestine, was introduced in clinical practice both in the United States and Europe in 2001. Since then, the use of SBCE has steadily increased with a broadening spectrum of clinical indications, and the most common application is the investigation of iron deficiency anaemia (IDA) and/or obscure gastrointestinal (GI) bleeding^[1-3]. Traditionally, obscure GI bleeding has been defined as overt or occult GI haemorrhage following normal upper and lower endoscopic examinations. However, the American College of Gastroenterology (ACG) recently challenged the current nomenclature, proposing that the term "obscure GI bleeding" should be reserved only for cases where a source of bleeding was not detected following conventional upper and lower GI endoscopic examinations and small bowel evaluation^[2]. Overt GI bleeding refers to patients presenting with either melaena or hematochezia, whereas occult GI bleeding refers to those presenting with IDA in the absence of visible blood loss to the patient or the physician, with or without guaiac-positive stools^[1].

The ACG recommends that SBCE should be performed as a first-line investigation for the examination of the small bowel, following visualisation of the upper and lower GI tract, although sometimes a second-look endoscopy may be indicated^[1]. Similarly, the British Society of Gastroenterology (BSG) in its recently published guidelines on the management of IDA recommended that following direct visualisation of the upper and lower GI tract, further assessment of the small bowel should be performed in the presence of symptoms indicating small bowel disease, or in cases where the haemoglobin level cannot be restored or maintained following iron replacement therapy. In these cases, evaluation of the small intestine is indicated, and this can be performed by SBCE, which has a diagnostic yield of 40%-55% and the advantage of being a minimally invasive endoscopic investigation, although other options include radiological investigations (Magnetic resonance imaging enteroclysis, computed tomography enterography, barium studies) or enteroscopy. Findings detected with SBCE are often within the reach of conventional endoscopes, hence a second-look gastroscopy (OGD) or colonoscopy may be of some value^[2]. In line with other institutional guidelines, the European Society of Gastrointestinal Endoscopy (ESGE) also recommends the use of SBCE as a first-line modality for the investigation of obscure

GI bleeding^[3].

ROLE OF SBCE IN THE INVESTIGATION OF OBSCURE GI BLEEDING

Up to 30% of patients investigated for IDA may remain without a definite diagnosis after evaluation of the upper and lower GI tract with conventional endoscopies and serological testing for coeliac disease^[4]. Similarly, in 5% of patients presenting with overt GI bleeding, a definite diagnosis is not reached after upper and lower GI endoscopy^[5]. The advent of SBCE reportedly led to the identification of a small-bowel culprit lesion in approximately two thirds of cases with 'obscure' GI bleeding^[6-13]. SBCE allows the evaluation of the entire small bowel in up to 90% of the patients, with a diagnostic yield of 38%-83% in patients with potential small bowel haemorrhage^[14]. SBCE has a high positive (94%-97%) and negative predictive value (83%-100%) in the evaluation of GI bleeding^[15-16]. Additionally, SBCE findings reportedly may lead to a therapeutic intervention or overall a change in clinical management in 37%-87% of cases^[16-17]. The main limitations of SBCE include a lack of specificity and a 10%-36% false-negative rate, as well as failure to identify the major duodenal papilla in a significant proportion of patients, which potentially could lead to important duodenal lesions being missed^[18-22].

Previous studies or anecdotal reports on SBCE referred to patients with non-small bowel lesions missed during preceding OGD or colonoscopy, indicating that these lesions were probably overlooked during conventional endoscopy. Non-small bowel lesions are defined as lesions proximal to the papilla of Vater and distal to the ileocaecal valve. The current study attempts to review all available studies in the literature and summarize their findings.

LITERATURE STUDY

An extensive bibliographical search was performed via the online databases PubMed and EMBASE. The keywords used were the following: non-small bowel lesions, capsule endoscopy, obscure GI bleeding, small bowel bleeding, unexplained IDA. All selected studies were manually examined to identify further relevant reports. This review included all original research papers published in full. Only those written or translated into English were included in the full text assessment. A subset of ten articles was relevant to this review.

NON-SMALL BOWEL LESIONS DETECTED BY SMALL BOWEL CAPSULE ENDOSCOPY

Kitiyakara *et al*^[23] reviewed a prospective database of 140 consecutive patients that were referred to a tertiary

University teaching hospital in Sydney, Australia, for further management of obscure GI bleeding. The referred patients had on average a mean of 2.3 OGDs and 2.2 colonoscopies, with no definitive diagnosis. Amongst them, 131 had small-bowel follow-through and 61 enteroscopy carried out^[23]. A definitive or likely cause of bleeding was identified in 66% of cases. Interestingly, in 6.4% the culprit lesion was within the reach of conventional endoscopy^[23]. Amongst patients with abnormalities in the upper GI tract, 3 women had gastric antral vascular ectasia (GAVE) and one had an inflammatory-appearing polyp. On the other hand, amongst patients with abnormalities identified distal to the ileocaecal valve, 2 were diagnosed with an adenocarcinoma of the caecum, one had a possible caecal tumour and 2 had an angiodysplasia of the caecum. In 5 out of 9 patients with non-small bowel lesions detected by SBCE, there was active bleeding at the time of the examination. Subsequently, all patients received appropriate management, based on the findings of the SBCE^[23].

In 2008, Elijah *et al*^[24] reported that amongst 201 consecutive SBCE performed in their centre for obscure GI bleeding between March 2003 and November 2004, 78 (38.8%) had a lesion that was within the reach of conventional endoscopy. All patients had at least one gastroscopy and colonoscopy carried out prior to the capsule endoscopy. The majority of patients were diagnosed either with erosions or vascular lesions (*i.e.*, angiectasias or GAVE). Amongst these patients, 21 had an endoscopic intervention carried out and one had surgery, as a result of the SBCE findings^[24].

Riccioni *et al*^[25] carried out a retrospective study to assess whether it is worthwhile performing SBCE in patients with unexplained IDA. About 138 patients (in a total of 650 consecutive patients) were investigated for unexplained IDA. In 2 out of 3 patients ($n = 91$), SBCE identified at least one gastric or small bowel lesion likely accounting for IDA. The SBCE findings in decreasing order of frequency included angiodysplasias (in 51 patients), jejunal and/or ileal micro-ulcerations (in 12), tumours (in 8), Crohn's disease, jejunal villous atrophy, erosive gastritis, a solitary ileal ulcer, and a small bowel polyp (in 1). In 4 patients blood was present in the lumen without visible mucosal lesions. Although the primary aim of this study was not the evaluation of SBCE in the detection of non-small bowel lesions, it is noteworthy that 4 patients were found to have unexplained IDA secondary to erosive gastritis, that surprisingly was not seen during OGD^[25]. At the end of the follow-up period, an improvement in haemoglobin levels after treatment (either medical, endoscopic or surgical) was reported, and complete resolution of IDA was achieved in 96.25% of patients with positive SBCE^[25].

Tachezi *et al*^[26] reported the results on 118 consecutive SBCE performed in two University hospitals for obscure GI bleeding. Overall, gastric lesions were detected in 37% of patients and were considered

significant (potentially haemorrhagic) in 21%. 17% of the detected lesions were underestimated or missed at conventional endoscopy. The most frequently detected lesions were haemorrhagic erosions. 10% of the lesions were identified as the source of GI bleeding^[26].

Vlachogiannakos *et al*^[27] published a study including 317 patients (out of 605 in total) who had SBCE performed for obscure (occult or overt) GI bleeding. The patients had a median of 2 OGDs and 2 colonoscopies before the SBCE^[27]. Interestingly, small bowel follow-through had also been performed in 114 patients and push enteroscopy in 84. A definite or likely cause of GI bleeding was found in 215 patients in the small bowel and in 11 cases (3.5%) the source of bleeding was outside the small bowel and within the reach of conventional endoscopes. Most non-small bowel lesions were identified in the caecum (7/11)^[27]. Of those 7 cases, 3 were diagnosed with a carcinoma of the caecum. Another patient had a bleeding diverticulum in the caecum (preceding colonoscopies had dismissed diverticular disease as a cause of overt bleeding due to the fact that no signs of bleeding were seen at the time of the examination). In addition, 2 patients had an angiodysplasia of the caecum and a young patient with anaemia, weight loss and bouts of abdominal pain, had multiple aphthoid ulcers in the caecum. This patient was later diagnosed with Crohn's disease. In this study, there were also 4 patients with non-small bowel lesions identified in the upper GI tract: 2 were diagnosed with angiodysplasia(s), one patient with longstanding anaemia and a medical history of scleroderma was diagnosed with GAVE (previously described as antral gastritis on repeated OGDs) and the last patient had a carcinoma of the cardia^[27]. Given the relatively low incidence of non-small bowel lesions detected by SBCE in this study (3.5%), the authors concluded that second-look endoscopy in a tertiary centre prior to SBCE would not be a cost-effective strategy and may in fact result in a delayed diagnosis^[27].

Hoedemaker *et al*^[28] prospectively collected data of consecutive SBCE studies performed in a tertiary-care centre in the Netherlands between 2003 and 2009. A total of 595 patients were included, the majority referred for obscure GI bleeding or suspected Crohn's disease. Most patients underwent conventional endoscopic examinations prior to referral for SBCE (mean number 1.1) and approximately 20% of patients had small-bowel-follow-through examination while about 10% underwent push enteroscopy^[28]. In 14.3% of patients, abnormalities were identified within the reach of OGD and colonoscopy, and only 2% of those lesions had been previously detected. The majority of the non-small bowel abnormalities were located in the terminal ileum ($n = 21$) and colon ($n = 19$), followed by abnormalities seen in the stomach ($n = 15$), the duodenum ($n = 12$), proximal jejunum ($n = 10$), and in other or multiple locations. The most frequent findings were angiodysplasias (37.6%), followed by erosions, active bleeding without definite mucosal pathology

and inflammatory lesions. Regarding patients originally referred for suspected Crohn's disease, abnormalities were seen in the terminal ileum in 33.6%. It is interesting that the terminal ileum had been previously intubated during colonoscopy in only about 30% of cases^[28]. The study however, was limited by the fact that follow-up data on patients diagnosed with a non-small bowel lesion at SBCE were lacking.

Riccioni et al^[29] prospectively reviewed data from 637 patients who underwent SBCE for obscure GI bleeding following a "normal" OGD and colonoscopy. 21.6% of these patients had a definite or likely cause of bleeding identified exclusively in the stomach, whereas 6.5% had a definite or likely cause in the colon; 21% had a combination of small bowel and non-small bowel lesions^[29]. Regarding patients with abnormal findings detected in the upper GI tract, 79/138 had multiple gastric and duodenal erosions, 11/138 had gastric or duodenal ulcers, 13/138 were diagnosed with GAVE, 11/138 with isolated or multiple angiodysplasias, 10/138 had multiple erosions in the distal duodenum (previously described as "non-specific duodenitis"), 8/138 were found to have inflammatory-appearing polyps and in the remaining patients (out of 138), SBCE documented the presence of fundic and esophageal varices, antral adenocarcinoma, neoplastic recurrence on gastric anastomosis, gastric leiomyoma, and spontaneous mucosal bleeding without visible lesions^[29]. Regarding patients with lesions identified in the lower GI tract, 24/41 were found to have isolated or multiple angiodysplasias in the caecum and/or ascending colon, and 8/41 had erosions or small ulcers at the ileocaecal valve or in the caecum. Of the remaining patients (out of 41), 3 had a haemorrhagic-appearing caecal mucosa without obvious lesions (all 3 were diagnosed with adenocarcinoma of the colon on repeat colonoscopy and were treated accordingly), 3 had non-specific "irregularity" of the mucosa of the right colon, 2 had a large bleeding caecal polyp and one patient had diverticular disease of the right colon with active bleeding^[29]. About 75.3% of patients with gastric lesions and 65.8% with colonic lesions did not have further presentations with obscure GI bleeding following diagnosis reached by SBCE and effective endoscopic and/or surgical management^[29].

Akin et al^[30] recently reviewed prospectively collected databases of patients referred to a tertiary teaching hospital in Turkey for potential small bowel bleeding, after inconclusive upper and lower conventional endoscopy. These patients were referred for SBCE and 114 met the inclusion criteria of the study^[30]. In 50% of cases a definite or likely cause of the bleeding was identified and amongst them, 8 patients (approximately 7%) were reported to have non-small bowel lesions within the reach of conventional endoscopy^[30]. The majority of these findings were identified in the caecum (5/8). Overall, 5 out of 8 patients had angiodysplasia(s) and 4 of them had active bleeding at the time of examination. In a patient with occult GI bleeding GAVE was found. Previous endoscopic examination of the

upper GI tract misdiagnosed the above finding as antral gastritis. In a patient with past medical history of Billroth II gastrectomy, active bleeding from an anastomotic ulcer was detected. Another patient had active bleeding distal to the duodenal bulb at the time of the SBCE examination, without a definitive lesion seen. A subsequent second-look endoscopy confirmed the presence of an angiodysplasia. Finally, a patient investigated for anaemia and abdominal pain was found to have a caecal ulcer on a caecal fold. A repeat colonoscopy with biopsies was performed and histologically "chronic active colitis" was shown^[30].

Juanmartíñena Fernández et al^[31] retrospectively analyzed data from 2217 consecutive SBCE performed in a tertiary centre in Spain between 2008 and 2016. 52.3% of the patients were referred for occult GI bleeding. The rest were referred for Crohn's disease, abdominal pain, chronic diarrhoea or other indications^[31]. SBCE detected gastroduodenal lesions in 566 patients. More than 80% had previously had 1.29 ± 1.1 (1-10) gastroscopies carried out, the vast majority within 30 mo prior to the SBCE. Among patients with gastric or duodenal lesions detected at SBCE, 75.4% and 86.4% respectively did not have these abnormalities found at prior endoscopies. Lesions identified more frequently in the stomach included erosions, vascular lesions and findings suggestive of chronic gastritis, while lesions found more frequently in the duodenum included erosions, erythema or vascular lesions^[31]. Lesions revealed by SBCE led to a change to the initial therapeutic strategy in 60.6% of the patients. In 12.8% an endoscopic intervention was carried out (most frequently argon plasma coagulation for vascular changes) and in 1.2% a surgical intervention was performed^[31]. Juanmartíñena Fernández et al^[32] also analyzed 526 consecutive SBCE performed in their centre between 2008 and 2011, in order to assess detection of colonic lesions identified at SBCE^[32]. Interestingly, 85.7% had a prior colonoscopy done within two years from the SBCE. Colonic abnormalities were detected in 47 patients (9%) and in 33 out of 47 cases synchronous small bowel lesion(s) were detected. In 66.6% out of them, capsule endoscopy identified findings, which had been overlooked during prior endoscopy. The most frequent findings were vascular lesions (41.8%) and colonic ulcers (20.8%). Treatment changes after SBCE led to an overall change to the initial therapeutic strategy in almost 60% of the patients^[32]. Findings are summarized in Table 1.

DISCUSSION

Obscure GI bleeding, either overt or occult, is a common presentation, encountered in 5%-10% of cases of GI bleeding^[30]. Conventional upper and lower GI endoscopy often fails to identify the source of bleeding and cannot visualise the entire GI tract. Similarly, radiology may detect small bowel masses and/or large ulcerating lesions but lacks sensitivity in detecting subtle mucosal

Table 1 Summary of publications studying non-small bowel lesions detected at capsule endoscopy

| References | Presentation (GI bleeding) | Mean duration (mo) ¹ | No of SBCE (n) | NSBL detection (n) | Most frequent site of NSBL | Most frequent lesion(s) |
|--|------------------------------|---------------------------------|----------------|--------------------|----------------------------|-----------------------------|
| Kitiyakara <i>et al</i> ^[23] | Obscure | 23.1 | 140 | 9 | Colon | GAVE |
| Elijah <i>et al</i> ^[24] | Obscure | Not specified | 201 | 78 | Only upper GI reported | Vascular lesions |
| Riccioni <i>et al</i> ^[25] ² | Occult | Not specified | 138 | Not specified | Not specified | Angiodysplasia |
| Tacheci <i>et al</i> ^[26] | Obscure | Not specified | 118 | 20 | Only upper GI reported | Erosions |
| Vlachogiannakos <i>et al</i> ^[27] | Obscure | 8.6 | 317 | 11 | Colon | Angiodysplasia and cancer |
| Hoedemaker <i>et al</i> ^[28] | Obscure | Not specified | 595 | 85 | Terminal Ileum | Angiodysplasia |
| Riccioni <i>et al</i> ^[29] | Obscure | Not specified | 637 | 179 | Stomach/ duodenum | Gastric - duodenal erosions |
| Akin <i>et al</i> ^[30] | Obscure | Not specified | 114 | 8 | Caecum | Angiodysplasia |
| Juanmartíñena Fernández <i>et al</i> ^[31] | Obscure or other indications | 19.8 | 2217 | 447 | Only upper GI reported | Erosions |
| Juanmartíñena Fernández <i>et al</i> ^[32] | Obscure or other indications | 25 | 526 | 24 | Only lower GI reported | Vascular lesions |

¹Mean duration of presenting symptom; ²Riccioni *et al*^[25] studied the role of small capsule endoscopy in investigating unexplained iron deficiency anaemia. SBCE: Small capsule endoscopy; NSBL: Non-small bowel lesion (defined as lesions within the reach of conventional upper and lower gastrointestinal endoscopy). This may include the terminal ileum; IDA: Iron deficiency anaemia; GI: Gastrointestinal.

abnormalities^[33]. Push enteroscopy identifies a potential source of bleeding in up to 40% of patients presenting with obscure GI bleeding. The main limitations of push enteroscopy are operator-dependency, the fact that it does not allow visualisation of the entire small bowel, and that it is an invasive procedure^[25].

The introduction of SBCE in clinical practice, a minimally-invasive modality of visualising the entire small bowel, led to the detection of a small-bowel source of obscure GI bleeding in approximately two thirds of cases^[6-13]. Another novel modality of visualising directly the small bowel is device-assisted enteroscopy (DAE). DAE includes double-balloon enteroscopy, single-balloon enteroscopy, spiral enteroscopy and balloon-guided endoscopy. DAE shares almost the same limitations as push enteroscopy, but has the advantage of real-time inspection of the lumen and the option of tissue sampling and endoscopic treatment if required^[3,24].

SBCE allows the evaluation of the entire small bowel in up to 90% of cases, has a diagnostic yield of up to 83% in patients with potential small bowel bleeding and its findings may lead to a change in management in 37%-87% of cases^[14-17]. Several comparative studies demonstrated SBCE superiority over barium follow-through (31% vs 5%)^[7], push enteroscopy (50% vs 24%)^[34], CT enteroclysis (59% vs 36%)^[35], intraoperative enteroscopy (74.4% vs 68%)^[36], and angiography (72% vs 56%)^[37]. In comparison to double-balloon enteroscopy, it has a similar diagnostic yield in detecting small-bowel lesions (55.3% vs 60.5%)^[38]. Thus, many gastrointestinal societies, such as ACG, BSG and ESGE recommend the use of SBCE as first-line investigation for obscure GI bleeding following normal OGD and colonoscopy^[1-3].

Until recently, the focus of most studies has been the actual findings within the small bowel. However, there has been increasing evidence suggesting that non-small bowel lesions detected by SBCE are sometimes within the reach of conventional endoscopy and have probably been missed at previous upper and lower GI endoscopy. In 2004, Tang *et al*^[39] reported that among 46 patients that underwent SBCE for obscure GI bleeding, 5 had a lesion likely overlooked during prior endoscopies^[39]. To the best of our knowledge, since then, there have only been very few studies published to date relevant to non-small bowel lesions overlooked by OGD and colonoscopy.

The reason why such lesions are often missed cannot be determined with confidence. A possible explanation for overlooking a non-small bowel lesion may be the small size or unusual site, posing a challenge in its detection. Additionally, air insufflated during conventional endoscopy may lead to suboptimal appearance of the lesion, as a consequence of vasculature compression, especially for vascular or subtle mucosal abnormalities. It is also interesting that in most studies included in this review, GAVE was misinterpreted as antral gastritis in a significant proportion of patients. In 2006, Sidhu *et al*^[40] reported 6 cases of GAVE detected during SBCE that were previously missed at conventional endoscopy, most frequently misdiagnosed as antral gastritis. In addition, luminal endoscopy performed in anaemic patients or in patients with low blood pressure may result in the findings being less prominent, especially if sedation is also administered. A non-bleeding lesion may also be harder to detect. As suggested by Kitiyakara *et al*^[23], SBCE may induce bleeding by traumatizing the mucosa which subsequently "reveals"

the lesion. With regard to colonoscopy, failure to reach the caecum either due to actual inability to reach it, or due to misidentification of the caecum by the endoscopist and premature termination of the endoscopy, may lead to missed pathology. Intubation of the ileocaecal valve and inspection of the terminal ileum also appears to be invaluable. Lesions behind colonic haustral folds and poor bowel preparation especially in the right colon are other possible explanations for missed lesions.

The prevalence of non-small bowel lesions missed at conventional endoscopy or push enteroscopy varied significantly between studies, from 3.5% to more than 30%^[23-32]. Vlachogiannakos et al^[27] report a statistically significant difference in the rates of such lesions being missed at endoscopy between different healthcare centres. In most studies, the relevant lesion was detected in the lower GI tract more frequently than in the upper GI tract. Regarding patients with overlooked lesions located in the upper GI tract, antrum is a frequent site where such lesions are found^[23-32]. Interestingly, colonic diagnoses were made using a SBCE, which is not designed to explore and examine the colon. Vascular lesions (either angiodysplasia or GAVE) were the most frequently detected abnormality. Other common findings included ulcers or erosions, tumours, polyps, inflammation, or GI bleeding due to diverticular disease. Although not assessed in all of the included studies, in the majority of patients the diagnosis was followed by interventional endoscopic or surgical treatment and/or conservative medical therapy. Treatment changes after SBCE most frequently included iron supplements, argon plasma coagulation for vascular lesions (angiodysplasia) and surgery for patients diagnosed with cancer. Lesions revealed by SBCE led to a change to the initial therapeutic strategy in up to 60% of patients^[31,32]. In one of the studies, an improvement in haemoglobin levels after treatment and complete resolution of IDA was achieved in more than 95% of patients with positive findings at SBCE^[25].

In conclusion, SBCE is a minimally-invasive endoscopic investigation that can accurately diagnose small bowel pathology, but often also detects abnormalities in the upper and lower GI tract that are within the reach of conventional endoscopy. The prevalence of such lesions that have been overlooked at conventional endoscopy is somewhat alarming, especially when considering the wide range of missed pathology that may include benign lesions, such as gastric or duodenal erosions, or significant abnormalities, such as malignant tumours. Great care should be taken in performing endoscopy carefully and under optimal conditions to maximize diagnostic accuracy and avoid unnecessary repeat examinations, leading to an increased cost and potentially hazardous delays in reaching a diagnosis. SBCE is a safe and reliable means of investigating further the GI tract, provided the procedure is carried out correctly and adequately trained healthcare professionals are interpreting the results. Our study is limited by the fact that most cases presented in the

literature, which are summarised in the current review, are retrospectively assessing patient data; therefore prospective studies are mandated to validate the findings.

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