



Digestive Endoscopy

Device assisted enteroscopy in the elderly – A systematic review and meta-analysis

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ABSTRACT

Background: Device assisted enteroscopy (DAE) is increasingly being carried out in elderly patients. This provides a challenge due to the underlying varied physiology and comorbidities these patients have.

Methods: We performed a systematic literature search for studies on elderly patients undergoing DAE. We calculated the pooled diagnostic (DY) and therapeutic yields (TY), major adverse events, length of small bowel examined and sedation administered. These were also compared to younger patients.

Results: Fourteen high quality articles on DAE in the elderly were included in this analysis (3289 total, 1712 elderly) patients. Nine of these studies were included in the final meta-analysis (681 elderly, 1577 young patients). The overall DY of DAE, double balloon enteroscopy (DBE) and single balloon enteroscopy (SBE) were 0.68 ($p=0.000001$), 1.74 ($p=0.0001$) and 1.90 ($p=0.009$). The TY of DAE, DBE and SBE were 0.45 ($p=0.00001$), 2.20 ($p=0.00001$) and 2.36 ($p=0.00001$). On comparison of elderly and young patients, DY (1.83; 95% CI: 1.49, 2.24; $p=0.00001$) and TY (2.28; 95% CI: 1.79, 2.89) were better in elderly patients. There was no difference in adverse events in both groups (2.16; 95% CI: 0.82, 5.69, $p=0.12$). Elderly patients were given less sedation than younger patients during DAE.

Conclusions: DAE has a higher DY and TY in the elderly than younger patients. DAE can be safely carried out in the elderly with less sedation.

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1. Introduction

Global life expectancy has increased by 5.5 years from 2000 to 2016 [1]. This has resulted in an increasing incidence of gastrointestinal diseases in the elderly population such as gastrointestinal malignancies and bleeding requiring diagnosis and follow up using endoscopic procedures. Endoscopy in the elderly can be challenging due to several reasons. Elderly patients struggle with the large volume of bowel preparation that might be required before certain endoscopic procedures because of underlying disorders such as chronic kidney disease and congestive heart failure. They are also more susceptible to side effects of medications due to underlying comorbidities such as cardiovascular disease [2]. Therapeutic endoscopic procedures are increasingly being preferred to surgical procedures as they are of lower risk than surgery especially in an elderly population [3,4] However, these are often prolonged procedures requiring sedation that still present a challenge in older patients.

Apart from bidirectional endoscopy, there is an increasing demand for device assisted enteroscopy (DAE) in the elderly to access pathology in the small bowel (SB) [5,6].

Double balloon enteroscopy (DBE) was first introduced by Yamamoto in 2001 [7]. This was followed by a different prototype with a single balloon – single balloon enteroscopy (SBE) [8]. Attempts have been made over the years to shorten the procedure time by the introduction of a helical overtube that could be used during deep enteroscopy – spiral enteroscopy (SPE) [9]. Data is mostly available for DBE as this technique has been available for the longest time. Our aim was to assess the diagnostic yield (DY) of DAE in elderly patients. Other secondary aims were to assess the safety of DAE, determine the therapeutic yield (TY), identify characteristics of the procedure, concordance with small bowel capsule endoscopy (SBCE) and explain indications and findings in those older than 65 years. Other aims were to compare DY, TY and other procedure related characteristics between elderly and young patients. These results will help gastroenterologists to make an informed decision on whether to carry out such procedures in elderly patients, an increasing demand that they very often have to face.

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1.1. Study selection

This manuscript was constructed in agreement with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria [10]. A thorough literature search was carried out using the Pubmed and Cochrane library (articles between January 2005 and June 2018). Mesh terms such as “Device assisted enteroscopy AND age OR elderly OR old”, “Double balloon enteroscopy AND age OR elderly OR old”, “Single balloon enteroscopy AND age OR elderly OR old” were used. More than one research criteria was utilised to prevent relevant articles from being missed. Potential relevant articles were identified and matched to the inclusion and exclusion criteria. References of these articles were also checked for any other relevant manuscripts. Initial selection was based on the title and abstract. Further selection was based on reading the whole article. The literature was performed by reviewer 1 (SCZ). Appropriate selection of articles was confirmed by a second reviewer (RS). In case of discrepancies, a third author (DS) acted as a referee in the adjudication process.

Manuscripts containing information on DAE (SBE and DBE) in elderly patients only or compared to younger cohorts of patients were included. Studies were included if they contained information on patient demographics such as the number of patients in each cohort studied, information on gender and DY of SB endoscopy in the elderly. The main information sought was indication for procedure, sedation used and procedure duration, diagnostic and TY of DAE, estimated length of SB examined and major complications patients experienced. In cases where there was missing or inadequate information, the individual authors were contacted.

1.2. Exclusion criteria

Studies including paediatric patients, letters to the editor, meta-analyses, case reports, case series, systemic and narrative reviews and abstracts with a full text in another language other than English were excluded.

1.3. Data items

- a) Major data items:
- b) Patient details: mean/median age and standard deviation, gender;
- c) Study details:
 - Retrospective or prospective, number of patients included, year, country, single or multicentre, type of DAE used.
 - Number of patients over and below the defined elderly age.
 - Number of patients with positive diagnosis at DAE.
- d) Indications for DAE.
- e) Minor data items:
- f) Number of patients who experienced adverse events secondary to DAE.
- g) TY of DAE.
- h) Findings at DAE.
- i) Length of SB examined.
- j) Duration of procedure.
- k) Concordance with SBCE.

Studies were included if all the major criteria were met. Authors were contacted if any of the major criteria were missing and were only included if these were provided. If some of the minor criteria were missing, authors were contacted to supply this information and were still included even if this information was not provided by the respective authors.

1.4. Risk of bias estimation

Risk of bias and methodological quality was assessed using the quality assessment of diagnostic accuracy studies (QUADAS) 2 scale [11,12]. The use of QUADAS 2 is recommended in systematic reviews to evaluate the quality of the studies and risk of bias. It consists of 4 key areas covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests and reference standard. The following sections were excluded as they were not applicable to this meta-analysis: Risk of bias & reference standard, applicability concern & index test, risk of bias & flow and timing. DY was the main reason for this meta-analysis and not test accuracy compared with a reference standard (Fig. 1).

Risk of bias was judged as “yes”, “no”, or “unclear”. If all answers to questions in a particular section were “yes” then risk of bias was judged as “low”. If any question was answered “no”, then this raised the question of the potential introduction of bias. Studies were considered high quality if they were low risk for at least 3 of the 4 questions. They were classified as low quality if they were at high or unclear risk of bias in 3 out of the 4 questions. Otherwise, they were classified as moderate quality.

1.5. Outcome measures

In this meta-analysis we assessed the yield of DAE (single balloon and double balloon enteroscopy) in elderly patients defined as an age of 65 years or older when compared to a younger population of patients [13]. Studies were also included if the median/mean age of the studied population was 65 years or older rather than 65 years being a cut off at which patients were included. A few studies that we included also defined old age as 70, 75 or 80 years. Secondly we also assessed, the TY of DAE in the elderly, different indications for enteroscopy, findings at enteroscopy, procedure details such as estimated length of SB examined, duration of procedure, sedation utilised, concordance with SBCE and the occurrence of adverse events.

1.6. Statistical analysis

Data on DY of DAE in the elderly were extracted from different studies and analysed using Revman 5.3 at 95% confidence interval. Heterogeneity of studies was estimated using Chi^2 and I^2 test. If I^2 values was between 30–60%, this represented moderate heterogeneity. If I^2 was 50%–90%, substantial heterogeneity was present and if this was 75%–100% considerable heterogeneity was present [14]. If heterogeneity was more than 30%, the random effects model (the DerSimonian–Laird method) was used. If not, the fixed effects model (the Mantel–Haenszel method) was applied. A p value of less than 0.05 represented heterogeneity between studies more than what could be expected due to chance alone.

The same programme was utilised to compare DY and other secondary factors mentioned above between elderly patients and younger patients. A p value of less than 0.05 was set to reflect a statistical significant difference between the 2 groups.

Forest plots were mainly used to represent the extracted data from the studies.

2. Results

Flow diagram 1 (Fig. 1) includes the detailed process of selecting suitable articles for this systemic review and meta-analysis. Ninety-nine articles were excluded after reviewing the title and abstract. This resulted in 20 potentially relevant articles of which the full articles were examined. Fourteen articles were included in

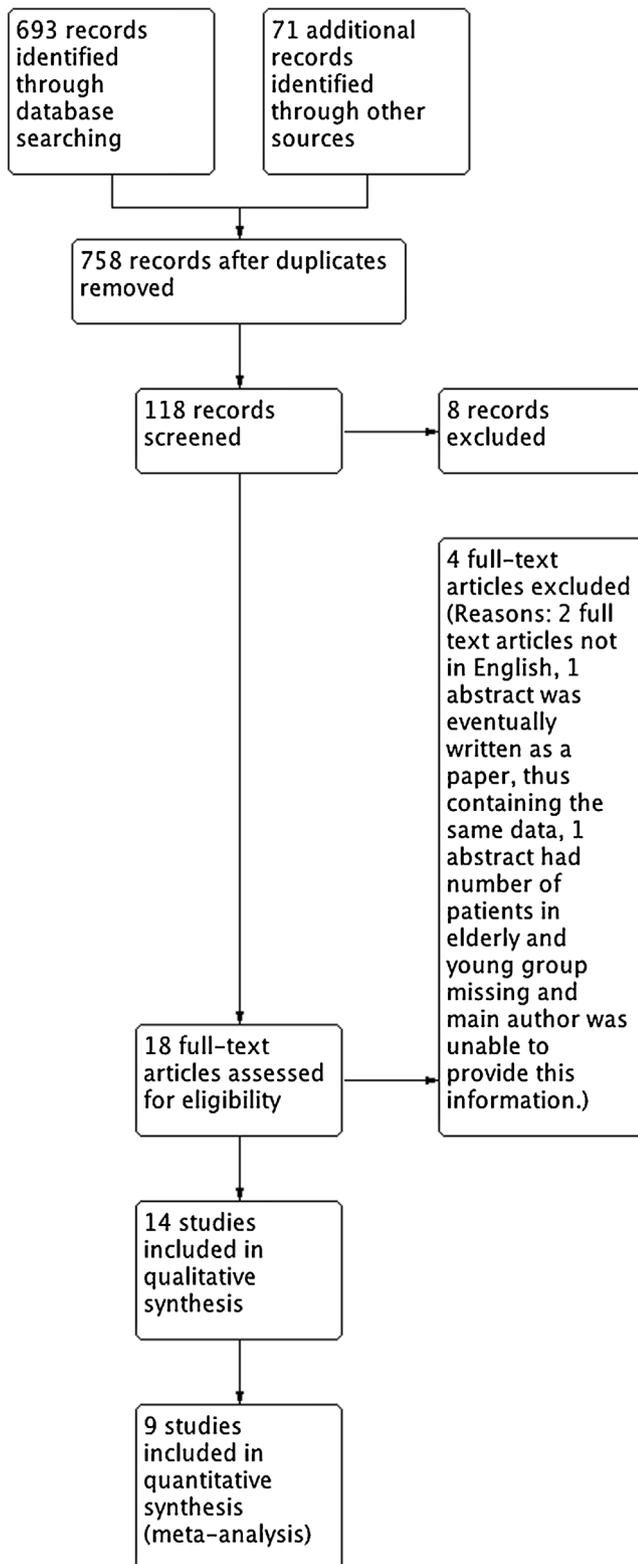


Fig. 1. Study flow diagram in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria.

the qualitative analysis. Nine of these studies were included in the final meta-analysis.

2.1. Study characteristics

Fourteen articles were included in this analysis with a total of 3289 (1712 elderly) patients [15–28]. Nine studies included both

elderly (681 patients) and young patients (1577) undergoing DAEs. This enabled a direct comparison between groups to be made. Another 4 studies included only elderly patients (1031 patients) (cut off of 65 years or higher) or the cohort studied had a mean age of 65 years or higher. Table 1 includes the main features of the studies included. Studies had a retrospective design except for 2. Patients underwent several types of DAE, namely single balloon and double balloon enteroscopy. All articles included were high quality studies as assessed by the QUADAS 2 questionnaire (Fig. S1, Supplementary section).

2.2. Risk of bias

All the 14 studies included were high quality studies as only 2 studies were at risk of bias in 1 domain each. This is because there was no clear age cut off for included patients but the mean age of the cohort was more than 65 years. This might have resulted in patients younger than the defined elderly age cut off being included.

2.3. Elderly patients

2.3.1. Diagnostic and therapeutic yield

The overall DY of DAE (1712 patients) in elderly patients was 0.68 (95% CI: 0.59, 0.76, $p=0.000001$). The pooled DY of DBE (1400 patients) and SBE (312 patients) were 0.67 (95% CI: 0.56, 0.78) (Fig. 2a) and 0.68 (95% CI: 0.63, 0.73) respectively. The overall TY (1712 patients) was 0.45 (95% CI: 0.39, 0.52; $p=0.00001$). The pooled TY of DBE (530 patients) and SBE (264 patients) were 0.46 (95% CI: 0.38, 0.54) (Fig. 2b) and 0.46 (95% CI: 0.40, 0.51) respectively.

2.3.2. Major adverse events

Major adverse events were defined as cardiovascular complications, acute pancreatitis, intestinal bleeding, perforation, aspiration pneumonia and death. The pooled major adverse events in patients undergoing DBE (1264 patients) was 0.02 (95% CI: 0.01, 0.03, $p=0.00001$) (Fig. 2c).

2.3.3. Procedure characteristics

The pooled length of SB examined (cm) in DBE (189 patients) was 186.23 (95% CI: -20.15, 392.62). The pooled duration of DBE (397 patients) in elderly patients was 95.28 (95% CI: 61.29, 129.26) (Fig. 2d). The pooled concordance of DBE with SBCE (446 patients) was 0.46 (95% CI: 0.24, 0.67) (Fig. 2e).

2.4. Elderly and young patients

2.4.1. Diagnostic yield

A subgroup analysis of studies that compared the DY of DAE between elderly (681) and young (1577) patients showed a DY of 1.83 (95% CI: 1.49, 2.24; $p=0.00001$) favouring elderly patients. A comparison of DBE between elderly (369 patients) and young patients (1208 patients) showed a DY of 1.74 (95% CI: 1.34, 2.27; $p=0.0001$) (Fig. 3a). The heterogeneity between these studies was low ($I^2=10\%$) and therefore a fixed model was used. Comparing studies that included both elderly (312 patients) and young (369) patients, the DY of SBE was 1.90 (95% CI: 1.17, 30.07, $p=0.009$). There was moderate heterogeneity between studies ($I^2=42$).

2.4.2. Therapeutic yield

Subgroup analysis in studies that included both elderly (497) and young (896) patients showed an overall TY of 2.28 (95% CI: 1.79, 2.89) favouring elderly patients. DBE (233 elderly vs 564 young patients) had a TY of 2.20 (95% CI: 1.59, 3.06, $p=0.00001$) (Fig. 3b). Heterogeneity was low ($I^2=17\%$) and the fixed effects model was used. Only 2 studies compared the TY of SBEs in the elderly (264)

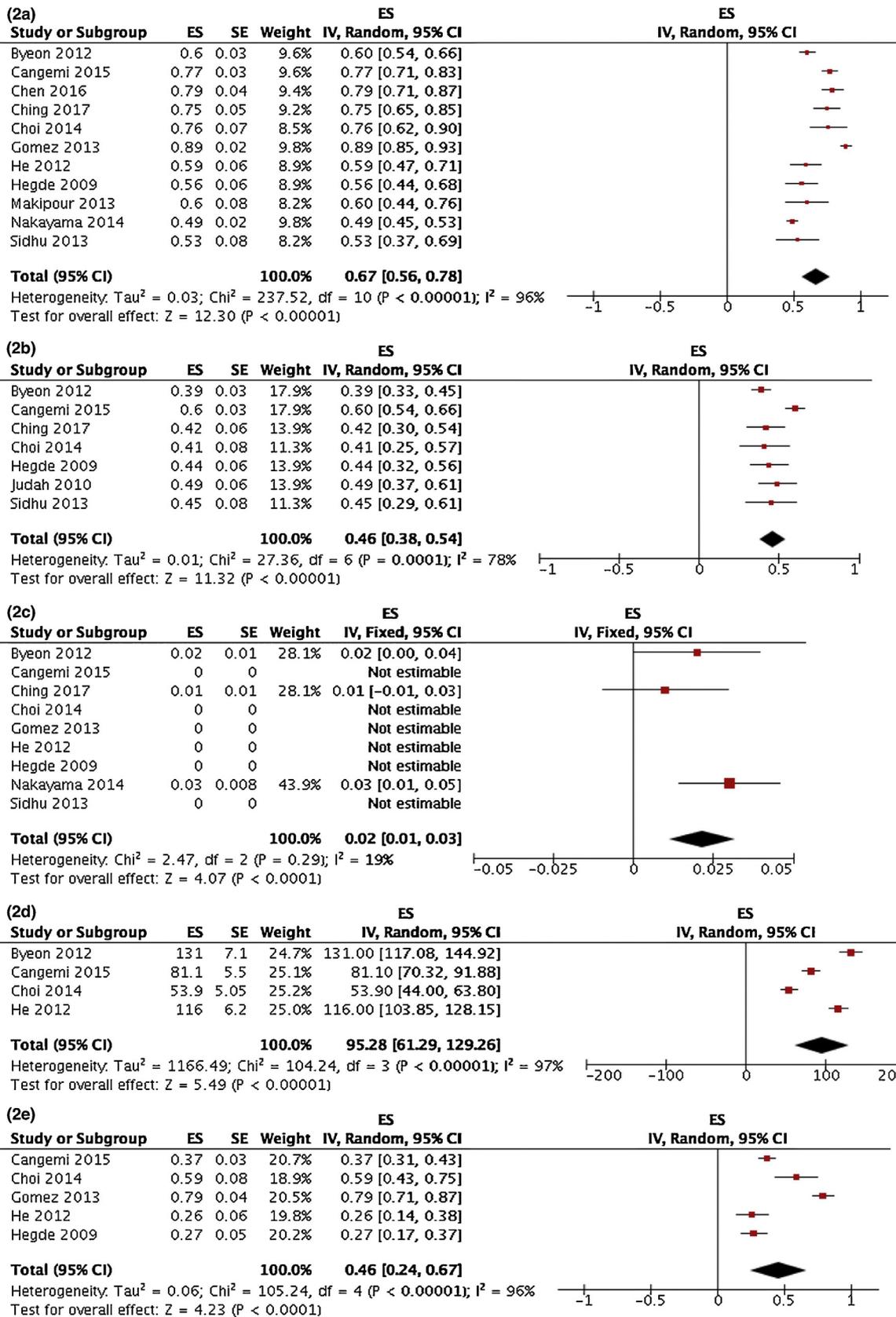


Fig. 2. (a) Forest plot: pooled diagnostic yield in patients undergoing double balloon enteroscopy; (b) forest plot: pooled therapeutic yield in patients undergoing double balloon enteroscopy; (c) pooled adverse events in patients undergoing double balloon enteroscopy; (d) forest plot of pooled duration of procedure (minutes) in elderly patients undergoing double balloon enteroscopy; (e) forest plot of concordance of double balloon enteroscopy with small bowel capsule endoscopy.

Table 1
Characteristics of studies included in this systematic review and meta-analysis.

Authors, year, ref	Prospective/retrospective	Elderly ± young	Number of elderly patients	Device assisted enteroscopy	Diagnostic yield in the elderly (%)	Therapeutic yield in the elderly (%)	Major adverse events (%)
Chang et al., 2017 [15]	retrospective	Both	56	SBE	75.0	39.3	1.13
Davis-Yadley et al., 2016 [16]	retrospective	Both	208	SBE	66.3	47.1	1.03
Lin, 2016 [17]	retrospective	Both	48	SBE	68.8		
Chen et al., 2016 [54]	retrospective	Both	94	DBE	78.7		
Ching, 2017 [28]	prospective	Both	73	DBE	75.3	42.5	0.47
Choi et al., 2014 [19]	retrospective	Both	41	DBE	75.6	41.5	0
Hegde, 2009 [20]	retrospective	Both	79	DBE	55.7	40.5	0
Sidhu, 2013 [21]	prospective	Both	40	DBE	52.5	45.0	0
Byeon et al., 2012 [22]	retrospective	Elderly	167	DBE	60.3	38.8	2.34
Cangemi, 2015 [23]	retrospective	Elderly	130	DBE	77.2	98.5	0
Gomez, 2013 [24]	retrospective	Elderly	137	DBE	89.2		0
He et al., 2012 [25]	retrospective	Elderly	59	DBE	68.6	60.8	0
Makipour, 2013 [55]	retrospective	Elderly	42	DBE	59.5		
Nakayama et al., 2014 [27]	retrospective	Elderly	538	DBE	48.5		3.2

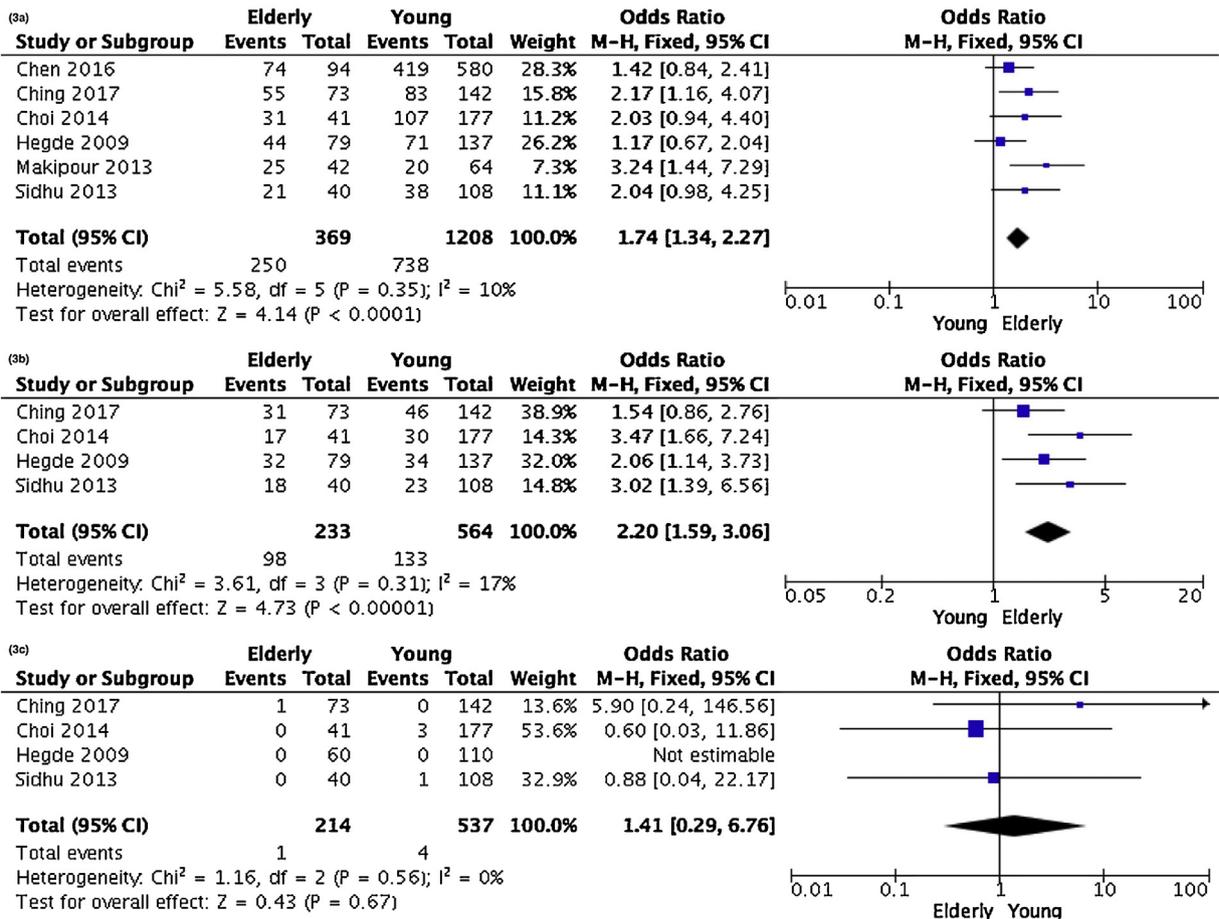


Fig. 3. (a) Forest plot of comparison: diagnostic yield in patients undergoing double balloon enteroscopy; (b) forest plot of comparison: therapeutic yield in patients undergoing double balloon enteroscopy; (c) forest plot of comparison: adverse events in patients undergoing double balloon enteroscopy.

and younger (332) patients: 2.36 (95% CI: 1.66, 3.35, $p = 0.00001$). Heterogeneity was absent in these studies.

2.4.3. Indications & findings

The most common indication for DAE in the elderly (78.8%) and young patients (71.6%) was obscure gastrointestinal bleeding. Suspicion of IBD (22.9%) was the second most common indication in the younger cohort of patients whereas suspicion of malignancy (13%) was the second commonest indication in the elderly (Table 2). Angioectasias were the most common findings in the

elderly (32.7%). Crohn's disease was the most common diagnosis in younger patients (37.1%) (Table 3).

2.4.4. Major adverse events

When comparing studies that included both elderly (478) and young (869) patients, the overall risk of major events was 2.16 (95% CI: 0.82, 5.69, $p = 0.12$). In patients undergoing DBE (214 elderly vs 537 young patients), the risk of major events was 1.41 and there was no statistical difference between the 2 groups (95% CI: 0.29, 6.76, $p = 0.67$). The fixed model was used as there was no hetero-

Table 2
Indications for device assisted enteroscopy in elderly and young patients.

Indication	Number of procedures for indication in the elderly	Total number of procedures in the elderly	% indication in the elderly	Number of procedures for indication in the young	Total number of procedures in the young	% indication in the young
Obscure gastrointestinal bleeding	386	490	78.8	604	843	71.6
Suspicion of a tumour	29	223	13.0	148	834	17.7
Suspected coeliac disease complications	6	73	8.2	1	142	0.7
Evaluation of abnormal imaging	3	79	3.8	20	137	0.1
Suspicion of IBD	15	264	5.7	232	1011	22.9

Table 3
Findings in the elderly and young at device assisted enteroscopy.

Findings	Number of procedures with findings in the elderly	Total number of procedures in the elderly	% indication in the elderly	Number of procedures with findings in the young	Total number of procedures in the young	% indication in the young
Angioectasias	213	651	32.7	244	1501	16.3
Tumours/polyps/mass	83	650	12.7	221	1501	14.7
Ulcers	69	516	13.4	64	764	8.4
Changes of coeliac disease	5	73	6.8	1	142	0.7
Strictures	12	321	3.7	14	470	3
Varices	8	209	3.8	0	118	0
Crohn's disease	10	94	10.6	215	580	37.1
Dieulafoy lesions	4	249	1.6	7	226	3.1
Peutz Jeghers syndrome	0	73	0.0	17	142	12

geneity between studies (Fig. 3c). Elderly patients undergoing SBE (264 elderly vs 332 young patients) had a pooled major adverse event rate of 2.81 (95% CI 0.78, 10.13) with no statistical significant difference between the 2 groups. ($p=0.12$). The fixed effect model was used as heterogeneity was 0%.

2.4.5. Procedure characteristics

Only 1 study compared the duration of DBE between elderly (47) and young (177) patients ($(55.9 \pm 25.5$ min vs. 58.6 ± 28.6 min; $p=0.347$) [19].

2.4.6. Sedation

In 1 study, elderly (73) patients undergoing DBE were given a mean of 12.4 mg/min of Propofol. Younger (142) patients were given 14.7 mg/min. In the same study elderly patients were given a mean of 84.7 mcg and younger patients were given a mean of 124.7 mcg of fentanyl when the procedure was carried out under sedation [28]. Comparing the amount of midazolam needed in patients undergoing DBE, the mean difference between the 2 groups (114 elderly vs 319 young) was -1.65 (95% CI: $-2.50, -0.81$). Elderly (41) patients given pethidine during DBE were given a lower dose $28.8 \text{SD} \pm 25.9$ when compared to younger (177) patients ($31.1 \text{mg} \pm \text{SD} 22.1$) ($p=0.565$) [19].

2.4.7. Concordance of device assisted enteroscopy with small bowel capsule endoscopy

The odds ratio of concordance between DBE and SBCE in elderly (120) vs young (314) patients was 1.94 (95% CI: 1.21, 3.12, $p=0.006$). There was no heterogeneity between studies ($I^2=0\%$). The concordance of SBE and SBCE in elderly (209) patients was 28.2% and that in younger (118) patients was 35.6% ($p=0.17$) [16].

3. Discussion

The pooled DY of DAE, DBE and SBE in this study were 0.68, 0.67 and 0.68 respectively. The pooled DY of DBE in the elderly was lower than that by Chen et al. (95% CI: 0.73; 0.66, 0.81) [18] and the

overall DY reported by Xin et al. 68.1% (95% CI, 64.3%–71.7%) [29]. The overall DY for SBE reported in the literature varies between 32.1% and 78% [30–35]. Our pooled DY for elderly patients undergoing SBE falls well within the range. A subgroup analysis of studies comparing the DY of DAE, DBE, and SBE between elderly and young patients showed a DY of 1.83, 1.74 and 1.90 respectively favouring elderly patients with a statistically significant difference. The DY for DAE favoured elderly patients over younger patients similar to the meta-analysis by Chen et al. [18] This is similar to the higher DY of SBCE in elderly patients when compared to younger patients [36].

The most common indication for DAE in the elderly was obscure gastrointestinal bleeding and the most common findings were angioectasias. This is in keeping with the published literature [5,37].

The pooled major adverse events in elderly patients undergoing DBE was 0.02. There was no significant difference in the occurrence of major adverse events in DBE and SBE between elderly and younger group of patients confirming that these procedures do not result in more complications when they are carried out in older patients. Our reported adverse events rate for elderly patients undergoing DBE is lower than that reported by the previous meta-analysis for elderly patients [18] and lower than the reported overall complication rate (0.72%–1.2%) [29,38]. No complications were reported in the literature during SBCEs except for 1 perforation during a SBE [30,33–35].

The pooled TY of elderly patients undergoing DAE, DBE and SBE were 0.45, 0.46 and 0.46 respectively. This is lower than the reported TY for DBE (up to 56.4%) [39–43] and higher than the TY of SBE (up to 30%) [34,40,41]. Both subgroup analysis for DBE and SBE favoured elderly patients over younger patients for TY similar to DY. This is possibly due to the higher incidence of angioectasias, ulcers and SB tumours in the elderly population [5,6]. Angioectasias are very often treated with argon plasma coagulation during DAE [44,45].

The duration of procedures was no different in the elderly to that in younger patients and consistent with the literature [46,31,47,48,49].

Elderly patients were overall given less sedation than younger patients during all types of DAEs in this study. Elderly patients are more likely to have significant comorbidities and hence at risk of cardiovascular events and aspiration pneumonia [50,51]. The recovery post sedation in this group is also prolonged due to the slower renal and hepatic clearance and a higher fat body mass. The American Society of Gastrointestinal Endoscopy (ASGE) hence recommends smaller doses of sedation to be given and that these should be titrated at a slower rate [52].

The concordance between DBE and SBCE in elderly patients was higher than in young patients. This is in keeping with the fact that elderly patients have a higher rate of positive findings on SBCE [36,53].

We excluded articles that were not in English, hence our results differ from the only other published meta-analysis by Chen et al. on DBE in the elderly [18]. The strengths of this study is portrayed by the inclusion of two modalities of DAE (DBE and SBE) unlike previous studies that have mainly concentrated on DBEs. All studies included were also high quality studies as determined by the QUADAS 2 questionnaire [12].

One limitation is the small number of studies on SBE in the elderly. Another limitation is that we included articles where the study population had a mean/median age of 65 years or older rather than 65 years being a cut off at which patients were included. This might have resulted in inadvertently including younger patients in the meta-analysis.

4. Conclusions

DAE has a higher DY and TY in the elderly compared to younger patients. It can be safely carried out without significant adverse events in a cohort of patients that is prone to complications due to their physiological changes. SB bleeding is the most common indication for DAE and angioectasias are the most commonly found pathology. Less sedation in elderly patients is used for DAE. This is in agreement with current guidelines for sedation in elderly patients during endoscopic procedures.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dld.2019.04.001>.

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