A systematic review and meta-analysis of disease severity and risk of recurrence in young versus elderly patients with left-sided acute diverticulitis

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A systematic review and meta-analysis of disease severity and risk of recurrence in young versus elderly patients with left-sided acute diverticulitis

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Young patients are thought to have a more severe disease course and a higher rate of recurrent diverticulitis. However, these understandings are mainly based on studies with important limitations. This review aimed to clarify the true natural history of acute diverticulitis in young patients compared to elderly patients. PubMed and MEDLINE were searched for studies reporting outcomes on disease severity or recurrences in young and elderly patients with a computed tomography-proven diagnosis of acute diverticulitis. Twenty-seven studies were included. The proportion of complicated diverticulitis at presentation (21 studies) was not different for young patients (age cut-off 40–50 years) compared to elderly patients [risk ratio (RR) 1.19; 95% confidence interval 0.94–1.50]. The need for emergency surgery (11 studies) or percutaneous abscess drainage (two studies) yielded comparable results for both groups with a RR of 0.93 (95% confidence interval 0.70–1.24) and 1.65 (95% confidence interval 0.60–4.57), respectively. Crude data on recurrent diverticulitis rates (12 studies) demonstrated a significantly higher RR of 1.47 (95% confidence interval 1.20–1.80) for young patients. Notably, no association between age and recurrent diverticulitis was found in the studies that used survival analyses, taking length of follow-up per age group into account. In conclusion, young patients do not have a more severe course of acute diverticulitis. Published data on the risk of recurrent diverticulitis in young patients are conflicting, but those with the most robust design do not demonstrate an increased risk. Therefore, young patients should not be treated more aggressively nor have a lower threshold for elective surgery just because of their age. Eur J Gastroenterol Hepatol 2020: 547–554

Introduction

As the prevalence of colonic diverticulosis increases with age from 20 to 30% of individuals younger than 50 years to over 70% in individuals over 80 years [1], the incidence of acute colonic diverticulitis follows this same pattern. Therefore, acute diverticulitis is most frequently evaluated in elderly patients. Nevertheless, some research specifically focusses on young patients with acute diverticulitis because it traditionally has been suggested that they suffer from a more severe disease course and a higher recurrent diverticulitis rate [2,3]. This may result in more aggressive treatment during the initial diverticulitis episode and a lower threshold for elective surgery to prevent future recurrent episodes. However, this supposedly altered disease course in young patients is mainly based on studies that have some important drawbacks. In most studies, the diagnosis acute diverticulitis was not based on findings on computed tomography (CT), which is essential to assure that patients with different diseases but with similar symptoms, such as irritable bowel syndrome or symptomatic colonic diverticulosis, did not enter the study [4,5]. Some population-based studies enter patients in their study population based on diagnosis coding in hospital registries which is even less accurate [6–8]. Recent studies use imaging proven diagnoses more often but lack a second important element when reporting recurrent diverticulitis rates: accounting for the length of follow-up per age group, thereby interfering with a reliable comparison of recurrence rates.

Previous systematic reviews were also affected by these limitations and included studies without a CT proven diverticulitis diagnosis and lacked studies that had taken the length of follow-up into account. Furthermore, despite the fact that one systematic review applied CT confirmation as inclusion criteria, two studies [9,10] without this CT confirmation had been included [11–13]. The present review provides a state of the art overview of current evidence on the natural history of young and CT proven

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acute diverticulitis patients, with focus on the more robust studies taking CT confirmation and length of follow-up into account.

Methods

Study identification

Two authors, S.T.v.D. and N.A., independently searched PubMed and EMBASE databases until April 2018 with the following search terms: diverticulitis, diverticular, age factors, age distribution, age, young, old and elderly (Supplemental Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A508*). No language limits were applied. Reference lists of obtained articles were reviewed for any omitted studies. MOOSE guidelines for reporting were followed [14]. A review protocol for this systematic review was not published or registered before this study was undertaken. Any disagreement during study selection, quality assessment or data extraction was resolved through discussion with each other.

Study selection

Studies that were considered for eligibility were randomized clinical trials, prospective or retrospective cohort studies and cross-sectional studies that reported outcomes of colonic diverticulitis patients in at least two age groups (apart from regression or survival analyses results) and whose diagnosis was proven by CT, pathology or surgery. Only studies including more than 75% left-sided diverticulitis patients were included in this review. Studies that did not report the number of left-sided diverticulitis patients were only included if they were conducted in a Western country, considering that Western patient cohorts are likely to have included predominantly left-sided diverticulitis patients, well above the limit of 75%. When studies were suggested to have overlapping cohorts, the largest of those studies was included in the review. When study cohorts were overlapping but different outcomes were reported, both studies were included. Studies that only included surgically treated patients or reported only postoperative outcomes, were excluded. Studies that included a selected group of patients not representative for the general diverticulitis population, such as only complicated diverticulitis patients when reporting on disease stage at presentation or only patients older than 70 years, were excluded. Reviews, letters, case reports and case series smaller than 10 patients were also excluded. The two reviewers independently considered all studies retrieved from the search for eligibility against these criteria.

Quality assessment

The two reviewers (S.T.v.D. and N.A.) critically appraised each study reporting rates of emergency surgery, percutaneous abscess drainage or recurrence using the Newcastle Ottawa Quality Assessment Scale for cohort studies [15]. Studies reporting disease stage at diverticulitis presentation were critically appraised using the Newcastle Ottawa Quality Assessment Scale for cross-sectional studies [15]. When studies reported on multiple outcomes, studies could therefore be assessed by both risk of bias tools.

Data extraction

The two reviewers (S.T.v.D. and N.A.) independently reviewed each included article. Each reviewer extracted the data on a predefined evidence table, after which the two tables were compared. Data collected from each article were study design and setting; in- and exclusion criteria for the study; applied age cut-off; proportion of left-sided diverticulitis patients; proportion of primary diverticulitis patients; crude results and results from regression or survival analyses for all outcomes in this review.

Outcome measures

The outcomes were divided into two categories; diverticulitis severity during the initial episode and risk of recurrent diverticulitis during follow-up. Outcomes covering the severity of the initial episode were stage of acute diverticulitis at presentation and need for emergency surgery or percutaneous abscess drainage during the initial diverticulitis episode. The stage of diverticulitis at presentation was defined as complicated (abscess or perforation) or uncomplicated. Recurrent diverticulitis could be diagnosed by either imaging or on clinical grounds, as reported by the studies.

Statistical analysis

The crude data of all outcomes were pooled and displayed using a forest plot and a random-effects model for each outcome. Results were reported as risk ratio (RR). Since the question whether age is actually associated with each outcome was considered more important than defining a precise age cut-off, all young age groups were analyzed together and all elderly groups were analyzed together despite the slight differences in age cut-offs that were used in various studies. Statistical heterogeneity was assessed using I^2. When heterogeneity reached above 70%, univariable meta-regression analysis was used to explore this heterogeneity. Meta-analyses were conducted using Review Manager (RevMan, version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014). Meta-regression analyses were conducted using SPSS, version 24.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Systematic review

The search retrieved 8443 studies and 3 studies were identified through reference lists of obtained articles. After removal of 2043 duplicates, titles and abstracts of 6403 studies were screened. A total of 448 full texts were screened for eligibility of which 27 studies were included in this review. The PRISMA flow diagram including reasons for exclusion of the studies that were screened full text is shown in Fig. 1.

Study characteristics

From the total of 27 included studies, 20 were conducted in Europe, six studies in the US and one study was conducted in the Dominican Republic (Table 1). Half of the studies (14 out of 27) only included left-sided acute diverticulitis patients, in five studies most patients suffered from left-sided diverticulitis (ranging from 77 to 98%),

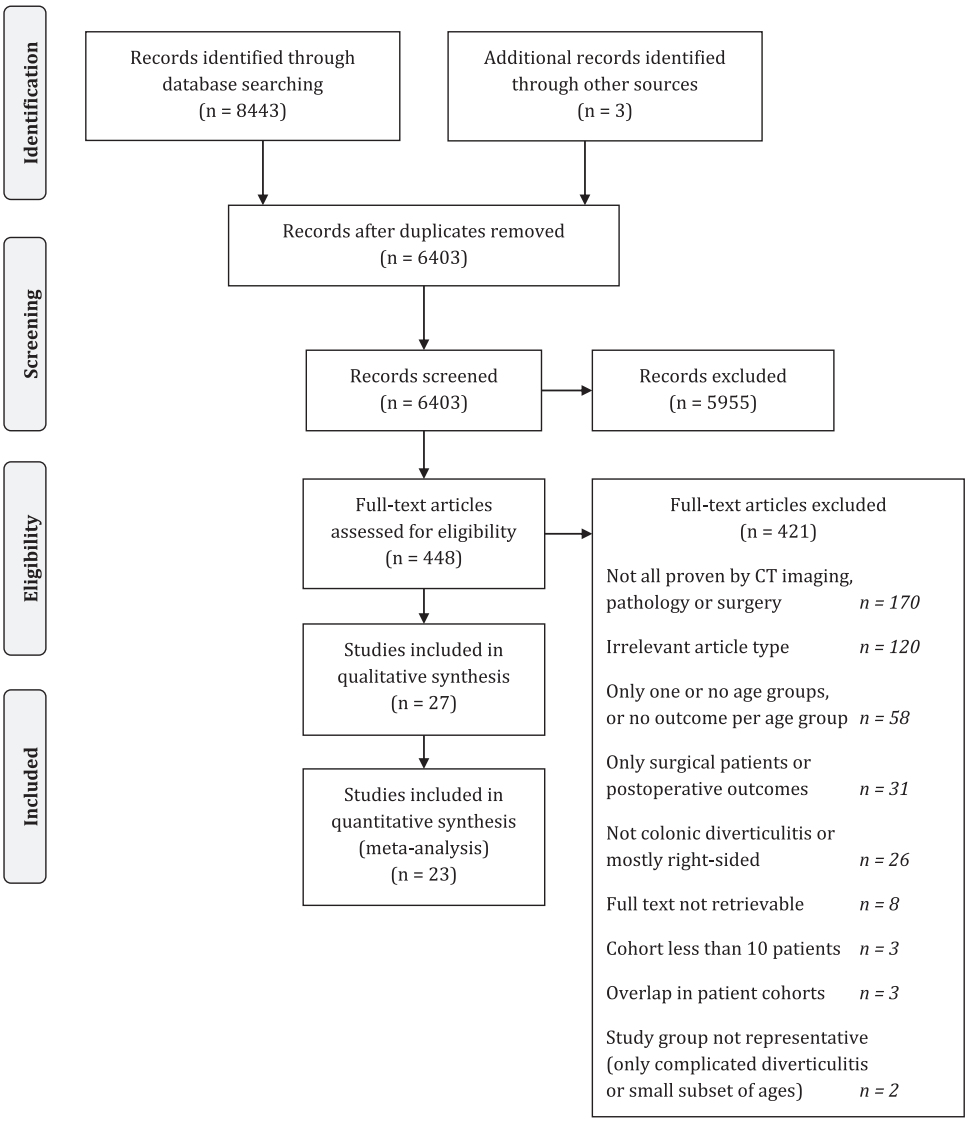

Fig. 1. PRISMA flow diagram [46].

and eight studies did not mention the number of left-sided diverticulitis patients. Not all studies used the same age cut-off to define the age groups. Most studies (17 studies) used 50 years as cut-off, some used 40 years (six studies) or 45 years (three studies), and one study reported a hazard ratio (HR) with age as continuous variable. Whereas most studies applied no explicit in- or exclusion criteria, five studies [16–20] that mainly focussed on the risk of recurrent diverticulitis only included a subgroup of patients such as only uncomplicated diverticulitis or only patients without colonic resection in the initial diverticulitis episode. The stage of acute diverticulitis at presentation was reported by 21 studies [20–40], rates of emergency surgery during the initial episode by 11 studies [18,24,27–29,32,34,37,39,41,42], rates of percutaneous abscess drainage during the initial episode by two studies [29,32] and rates of recurrent diverticulitis by 12 studies [16–20,24,25,27,33,34,36,41].

Critical appraisal

For the stage of diverticulitis at presentation, some bias might have been introduced by the retrospective design of 10 out of 21 studies (Supplemental Tables 2 and 3, Supplemental digital contents 2 and 3, *http://links.lww.com/EJGH/A509*; http://links.lww.com/EJGH/A510). A clear description of reasons for interventions was lacking in most studies reporting need of emergency surgery or percutaneous abscess drainage. Thresholds for performing an intervention likely differed between studies and therefore the number of interventions varied widely between studies. For the outcome recurrent diverticulitis, an important potential bias is the lack of description of length of follow-up in various age groups in the majority of studies. The number of patients with recurrent diverticulitis is mostly affected by the length of the study period in which a recurrence could have occurred. Therefore, it is essential to know whether both age groups had comparable follow-up durations in order to interpret the results.

Severity of diverticulitis at presentation

A total of 21 studies [20–40] reported results of severity of diverticulitis at presentation. Twenty studies including 7477 patients reported crude data and were pooled (Fig. 2). Young age was not associated with higher risk of

complicated diverticulitis at presentation; pooled RR 1.19 [95% confidence interval (CI) 0.94–1.50]. However, heterogeneity was substantial (I^2 86%). Univariable meta-regression was used to explore this heterogeneity by testing four study characteristics that could be extracted from the studies with this outcome. Neither of these variables could explain this heterogeneity; type of age cut-off (50 years versus 40 years; coefficient 0.134, $P = 0.601$), study design (prospective versus retrospective; coefficient 0.130, $P = 0.569$), history of diverticulitis (only primary diverticulitis versus mixed with history of diverticulitis; coefficient 0.204, $P = 0.360$) and location of diverticulitis (100% left-sided diverticulitis versus partially left-sided diverticulitis or not reported; coefficient –0.116, $P = 0.618$). Four studies [28,36,38,39] reported results from multivariable logistic regression analyses. Two of these four studies did not report crude results but only reported that age below 40 was not a risk factor for free perforation or complicated diverticulitis [36,39]. The third study reported a slightly increased odds ratio (OR) for every 10-year increase of age (adjusted OR 1.16; 95% CI 1.01–1.33) [38]. The fourth study found comparable risks for both groups (adjusted OR 1.01; 95% CI 0.65–1.57) [28].

Need for emergency surgery or percutaneous abscess drainage

A total of 11 studies [18,24,27–29,32,34,37,39,41,42] reported need for emergency surgery within the initial diverticulitis episode. Ten studies [18,24,27–29,32,34,37,39,42] including 4115 patients reported crude data and were pooled. Young age was not associated with the need for emergency surgery (pooled RR 0.93; 95% CI 0.70–1.24; I^2 45%) (Fig. 3). One study [41] reported no crude data but a non-significantly higher odds for elderly patients (OR 1.79; 95% CI 0.78–4.10). The need for percutaneous abscess drainage was reported in only two studies [29,32] (907 patients), yielding comparable risks in both age groups (pooled RR 1.65; 95% CI 0.60–4.57; I^2 0%) (Fig. 4).

Recurrent diverticulitis

A total of 12 studies [16–20,24,25,27,33,34,36,41] reported rates of recurrent diverticulitis after a documented episode of acute diverticulitis. Eight studies [17,18,24,25,27,33,34,36] including 1489 patients reported crude results and were pooled (Fig. 5). Young patients were at significantly higher risk for recurrent diverticulitis compared to elderly patients (pooled RR 1.47; 95% CI 1.20–1.80; I^2 0%). The length of follow-up per age group was not reported in almost all studies, only the small study of Pisanu *et al.* [36] reported comparable follow-up durations in both groups.

Therefore results from four studies [16,19,20,41] more robustly reporting regression and survival analyses, were reviewed. All four studies demonstrated that age was not a risk factor for recurrence (Table 2). One of these four studies found a non-significantly lower risk for recurrent diverticulitis in patients younger than 40 years (adjusted OR 0.78; 95% CI 0.48–1.28) [41]. More importantly, the other three studies used survival analyses and reported HRs in which, in contrast with crude data or ORs, length of follow-up was taken into account. Two out of these three studies found no association between age (as continuous variable) and recurrent diverticulitis; HR 0.99 (95% CI 0.96–1.01) and HR 1.00 (95% CI 0.997–1.02), respectively [16,19]. The third study found a non-significantly lower risk of recurrent diverticulitis in patients younger than 50 years (adjusted HR 0.62; 95% CI 0.38–1.00) [20].

Discussion

This systematic review and meta-analysis demonstrates that young patients with acute diverticulitis do not have a more severe disease course and probably do not have an increased risk of recurrent diverticulitis compared to elderly patients. Young patients do not have a higher proportion of complicated diverticulitis at presentation. Although heterogeneity in this comparison is substantial, along with the comparable rates of need for emergency surgery and percutaneous abscess drainage one can conclude that young patients do not appear to suffer from a more virulent course of an acute diverticulitis episode. Meta-analysis of crude data on recurrent diverticulitis shows a significant 47% higher risk for young patients. However, description of length of follow-up per age group was lacking in all but one studies. For an outcome measure that relies mostly on the length of the observation period in which an event could have occurred, equal follow-up durations are essential. Three studies with the most robust design by taking length of follow-up duration into account, using survival analysis and HRs, found no association between age and risk of recurrence or even a non-significantly lower risk of recurrence in young patients.

Nowadays, while in many ways a more conservative approach has been implemented for acute diverticulitis, young patients have been suggested to differ from elderly patients regarding disease severity and risk of recurrences. Therefore, a lower threshold for more aggressive treatment or elective surgery has been put forward. Since more recent studies show that young patients may not differ from elderly patients, some guidelines do no longer recommend elective resection based on age [43–45]. However, uncertainty remains and most guidelines still conclude that the risk of recurrent diverticulitis appears to be higher in young patients and consequently recommendations are formulated with caution.

A strength of this systematic review is the broad search strategy that identified several studies that were not identified by earlier systematic reviews. Furthermore, numerous more recently published studies could be included, so that even with strict inclusion criteria a considerable number of studies were included. Another strength is that this review did not only focus on crude data but assessed regression and survival analyses results as well, which appear to provide more robust information on the natural course of acute diverticulitis in young patients.

Some limitations should be considered. Comparison of the severity of diverticulitis at presentation was hampered by substantial heterogeneity which additional meta-regression analysis could not explain. This heterogeneity was probably caused by differences in patient characteristics between countries, differences in CT scanners, and differences in interpretation by radiologists. Moreover, the influence of selection bias in study inclusion cannot be ruled out completely. Also, most studies did not define

Table 1. Summary of included studies

Study	Design	Selection and definitions: Patient selection	Age cut-off	Left-sided	Only primary	Reported outcome(s): Stage at presentation	Emergency surgery	Percutaneous drain	Recurrence
Al-Sahaf *et al.* (2008) [21]	Retro	None	50	100%	NR	X			
Ambrosetti *et al.* (1998) [22]	Pros	None	50	100%	Yes	X			
Bose *et al.* (2013) [41]	Retro	None	50	NR	Yes		X		X
Buchs *et al.* (2013) [16]	Pros	Only uncomplicated diverticulitis	None	100%	Yes				X
Chautems *et al.* (2002) [23]	Pros	None	50	100%	Yes	X			
Faria *et al.* (2011) [24]	Retro	None	50	100%	Yes	X	X		X
Frileux *et al.* (2010) [25]	Retro	None	50	100%	Yes	X			X
Hall *et al.* (2010) [26]	Retro	None	50	98%	Yes	X			
Hjern *et al.* (2008) [27]	Retro	None	50	96%	Yes	X	X		X
Holmer *et al.* (2011) [28]	Pros	None	40	100%	No	X	X		
Holmer *et al.* (2011) [17]	Pros	No perforation, stenosis or fistula	50	100%	No				X
Horesh *et al.* (2016) [29]	Retro	None	50	94%	Yes	X	X	X	
Kaiser *et al.* (2005) [30]	Pros	None	40	NR	No	X			
Kijsirich-areanchai *et al.* (2015) [42]	Retro	None	40	77%	NR		X		
King *et al.* (2015) [31]	Retro	None	40	NR	No	X			
Kotzam-passakis *et al.* (2010) [32]	Retro	None	50	100%	No	X	X	X	
Lahat *et al.* (2013) [33]	Pros	None	45	NR	Yes	X			X
Lopez *et al.* (2012) [34]	Pros	None	45	100%	Yes	X	X		X
Mäkelä *et al.* (2015) [35]	Pros	None	50	NR	Yes	X			
Nelson *et al.* (2008) [18]	Pros	Only complicated diverticulitis	50	NR	No		X		X
Pisanu *et al.* (2013) [36]	Pros	None	50	NR	No	X			X
Poletti *et al.* (2004) [37]	Retro	None	50	100%	NR	X	X		
Ritz *et al.* (2011) [39]	Pros	None	40	100%	No	X	X		
Ritz *et al.* (2011) [38]	Pros	None	40	100%	No	X			
Sallinen *et al.* (2015) [19]	Retro	Only patients without initial resection	45	NR	No				X
Trenti *et al.* (2015) [20]	Pros	Only patients without initial resection	50	100%	Yes	X			X
Zaidi *et al.* (2006) [40]	Retro	None	50	83%	No	X			

NR, not reported; Pros, prospective cohort study; Retro, retrospective cohort study.

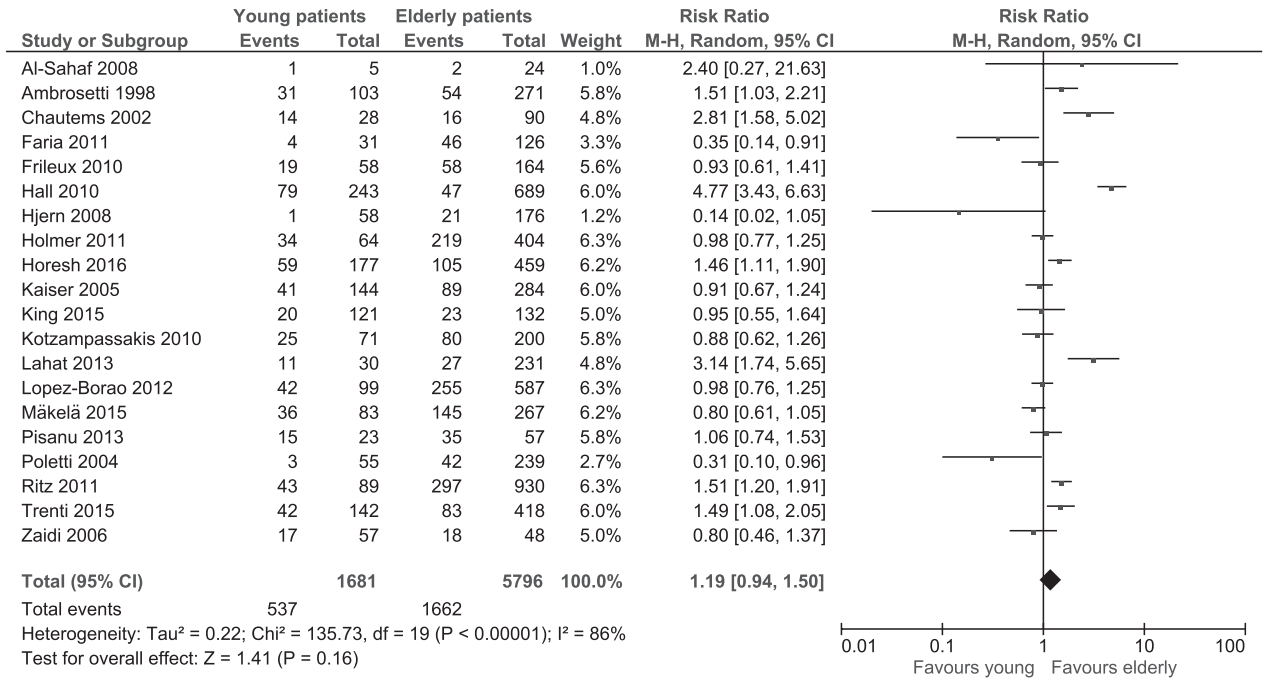

Fig. 2. Forest plot of risk ratios for complicated diverticulitis (abscess or perforation) at initial presentation in young and elderly acute diverticulitis patients.

their reasons to perform emergency surgery or percutaneous abscess drainage. Therefore, it remains unclear whether these patients were operated on because of clinical worsening or that in some studies patients also underwent emergency surgery for persistent complaints or bowel obstruction. The latter is most likely given the wide range of emergency surgery rates across studies. Although interpretation of the risk of recurrent diverticulitis was improved by looking at results of survival analyses, which solved the major drawback of lack of follow-up description in both age groups, another limitation regarding recurrent diverticulitis results should be taken into account. Most

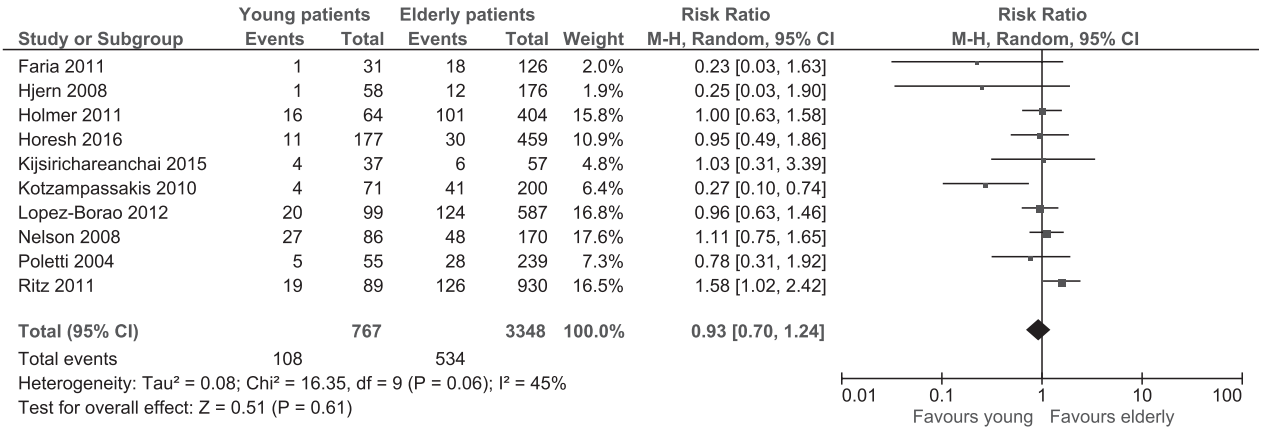

Fig. 3. Forest plot of risk ratios for emergency surgery within initial episode of acute diverticulitis in young and elderly acute diverticulitis patients.

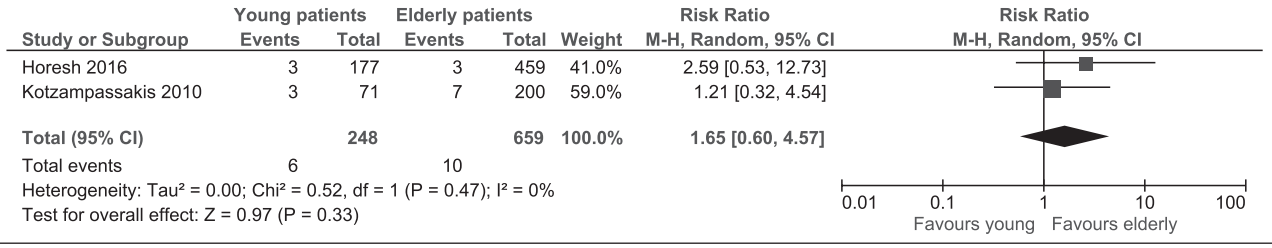

Fig. 4. Forest plot of risk ratios for percutaneous abscess drainage within initial episode of acute diverticulitis in young and elderly acute diverticulitis patients.

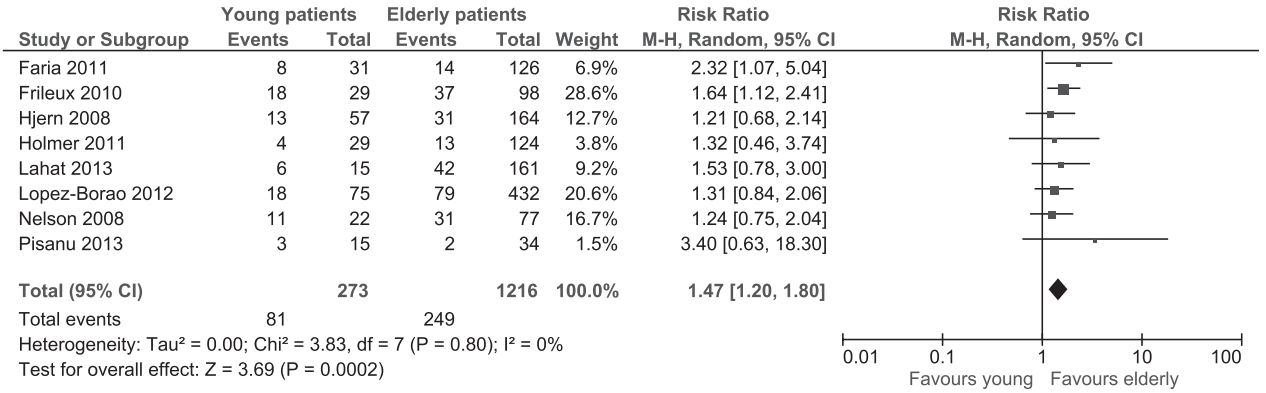

Fig. 5. Forest plot of crude risk ratios for recurrent diverticulitis in young and elderly acute diverticulitis patients.

Table 2. Results from reported univariable or multivariable regression or survival analyses

	Study	Effect estimate	Interpretation
Complicated diverticulitis at presentation	Holmer *et al.* (2011) [28]	Age <40: adjusted OR 1.01 (95% CI 0.65–1.57)	Age below 40 no risk factor for free perforation in multivariable analysis
	Ritz *et al.* (2011) [39]	Not reported	Age below 40 risk factor for free perforation in univariable analysis, but no risk factor in multivariable analysis
	Ritz *et al.* (2011) [38]	Continuous age with 10-year increase: adjusted OR 1.16 (95% CI 1.01–1.33)	Increased risk of free perforation in multivariable analysis for every 10-year increase of age
	Pisanu *et al.* (2013) [36]	Not reported	Age below 40 no risk factor for complicated diverticulitis in multivariable analysis
Emergency surgery within initial episode	Bose *et al.* (2013) [41]	Age >50: OR 1.79 (95% CI 0.78–4.10)	Age over 50 no risk factor for emergency surgery in univariable analysis
Recurrent diverticulitis	Bose *et al.* (2013) [41]	Age <40: adjusted OR 0.78 (95% CI 0.48–1.28)	Age below 40 no risk factor for recurrence
	Buchs *et al.* (2013) [16]	Continuous age: HR 0.99 (95% CI 0.96–1.01)	Age no risk factor for recurrence
	Sallinen *et al.* (2015) [19]	Continuous age: HR 1.0 (95% CI 0.997–1.02)	Age no risk factor for uncomplicated recurrence
	Trenti *et al.* (2015) [20]	Age <50: adjusted HR 0.62 (95% CI 0.38–1.00)	Age below 50 no risk factor for recurrence

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

studies did not state the diagnostic modalities that were used to diagnose a recurrent episode. When, for instance, recurrent diverticulitis is diagnosed on clinical grounds only, one can imagine that differences between young and elderly patients can occur by differences in presentation of complaints or lower thresholds for CT in elderly patients.

Notwithstanding the substantial heterogeneity in the comparison of diverticulitis severity at initial presentation, meta-analyses results of the need for emergency surgery and percutaneous abscess drainage support the conclusion that young patients do not suffer from a more severe disease course. Furthermore, studies with the most robust design did not find an association between age and risk of recurrent diverticulitis. Therefore, age should not be considered a reason for more aggressive treatment of an acute diverticulitis episode or a lower threshold for elective sigmoid resection in the prevention of recurrent diverticulitis compared to elderly patients. Obviously, younger patient may have different demands because of working activities or physically demanding hobbies compared to elderly patients. These kinds of individual patient-related factors can lower the threshold for elective surgery, but young age itself should not be a reason for more aggressive or more invasive treatment. Although the need for emergency surgery and percutaneous abscess drainage do inform us on the course of disease after the initial diverticulitis diagnosis in the various age groups, prospective evaluation of the variable 'age' on disease progression or need for interventions after an initial diagnosis of uncomplicated diverticulitis has not been performed extensively.

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Conflicts of interest

There are no conflicts of interest.

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