Alpha-1-antitrypsin deficiency (carrier) as possible risk factor for development of colonic diverticula. A multicentre prospective case–control study: the ALADDIN study

S. J. Rottier*†‡, L. C. Dreuning†, J. van Pelt§, A. A. W. van Geloven†, X. D. Y. Beele¶, P. M. Huismans¶, W. Y. Deurholm**, C. A. Rottier*, K. van Leeuwen††, M. de Boer††, G. van Mierlo‡‡, M. A. Boermeester‡, W. H. Schreurs* for the ALADDIN Collaborative Study Group*

*Department of Surgery, Northwest Clinics, Alkmaar/Den Helder, The Netherlands, †Department of Surgery, Tergooi Hospital, Hilversum, The Netherlands, ‡Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands, §Department of Clinical Laboratory, Northwest Clinics, Alkmaar/Den Helder, The Netherlands, ¶Department of Radiology, Tergooi Hospital, Hilversum, The Netherlands, **Department of Radiology, Northwest Clinics, Alkmaar/Den Helder, The Netherlands, ††Department of Molecular and Cellular Hemostasis, Sanquin Blood Supply, Division Research and Landsteiner Laboratory of the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and ‡‡Department of Immunopathology, Sanquin Blood Supply, Division Research and Landsteiner Laboratory of the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Received 29 March 2020; accepted 21 June 2020; Accepted Article online 15 July 2020

Abstract

Aim Connective tissue changes due to ageing or diseases leading to changes in the colonic wall are one theory for the development of diverticula. Alpha-1-antitrypsin (A1AT), a protease inhibitor that protects connective tissue, possibly plays a role in the aetiology of diverticulosis. The aim of this study was to explore associations between the development of diverticula and A1AT deficiency.

Methods This was a multicentre prospective case–control study. A total of 221 patients aged ≥ 60 years with acute abdominal pain undergoing abdominal CT were included and analysed. Patients with diverticula were defined as the research group, patients without diverticula as controls. Genotype analysis for A1AT deficiency was performed.

Results Twenty-six of 221 (11.8%) patients were diagnosed with (being a carrier of) A1AT deficiency. A non-significant difference in prevalence between patients with and without diverticula was found, 20 (13.9%) of 144 vs 6 (7.8%) of 77, respectively, with a crude OR of 1.9 (95% CI 0.7–5.0; P = 0.186) and after adjustment for confounders an adjusted OR of 1.5 (95% CI 0.5–4.0; P = 0.466). A non-significant difference in 30-day mortality rate from acute diverticulitis between A1AT deficient patients (or carriers) and those without was observed: two (22.2%) of nine patients with A1AT deficiency vs 1 (1.8%) of 55 without.

Conclusion We found no convincing evidence that A1AT deficiency plays a role in the aetiology of diverticulitis, although deficient patients and carriers had a higher mortality when experiencing diverticulitis. Diverticulitis is a multifactorial disease and larger numbers may be needed to explore the role of A1AT deficiency among other contributing factors.

Keywords Alpha-1-antitrypsin, connective tissue disease, diverticula, diverticulitis, diverticulosis

What does this paper add to the literature? Primarily in case reports, connective tissue diseases have been mentioned as a risk factor for diverticulitis. Furthermore, connective tissue changes due to ageing or diseases may lead to changes in the colonic wall and development of diverticula. The present study explores associations between connective tissue, diverticula and diverticulitis. This knowledge may open new possibilities for prevention or treatment.

Introduction

The incidence of colonic diverticulitis increases with age and is primarily a disease amongst the western population. When searching the literature for possible risk
factors for the development of diverticula, diet, obesity and alcohol consumption are often mentioned [1–3]. For the development of acute diverticulitis medication such as corticosteroids, smoking and hereditary factors are possible risk factors [4–6]. However, the true underlying pathophysiological mechanism that leads to the formation of colonic diverticula remains unclear. Common theories about the aetiology causing colonic diverticula are the influence of diet, specifically the lack of fibre in the western diet, and the microbiome theory [2,7,8].

In the published study protocol of the present study (ALADDIN study) [9], the hypothesis of the onset of diverticula being the result of an age-related disorder was described in further detail. In summary, ageing eventually leads to alteration of the colonic epithelium which induces a decrease in colonic wall strength, partly due to changes in the collagen structure [10,11]. A pathology study found that colonic collagen from subjects affected by colonic diverticulosis had a higher number of crosslinks than subjects with unaffected colonic tissue, illustrating that these structural changes have a greater impact than the changes as part of the natural ageing process [12]. Also, an increase of the less stable number of crosslinks than subjects with unaffected colonic wall. One specific feature that could play a role in the development of diverticula is alpha-1-antitrypsin (A1AT) deficiency, a hereditary disorder which affects individuals of all racial subgroups worldwide. In Europe, the prevalence of A1AT deficiency is 0.24%, whereas the prevalence of A1AT carriers is approximately 8% [16]. A1AT is a protease inhibitor which protects the connective tissue of the lungs when elastase is released [17,18]. Collagen types I and III give the alveolar wall of the lungs its structural form; MMPs that are involved in tissue repair and remodelling try to maintain this wall structure [19–21]. Some of the same MMPs involved in connective tissue metabolism are altered in patients with lung emphysema as well as in patients with (complicated) diverticular disease [21,22]. In patients with A1AT deficiency, specifically individuals with type PiZZ, mortality was increased due to respiratory and hepatic disease and pulmonary embolism, compared to a population without this pathological allele for A1AT, as expected. Patients with this deficiency also had a higher mortality due to complicated colonic diverticulitis, which supports the hypothesis that A1AT could be associated with the development of diverticula and (complicated) diverticulitis [23].

**Method**

**Study design and population**

The trial protocol (rationale, design and population) has been published [9]. Here, we summarize the most important details. In this multicentre, prospective, case–control study (ALADDIN study) patients were included from three non-academic hospitals in the Netherlands. All patients ≥60 years with acute abdominal pain who had undergone an abdominal CT were recruited from the Emergency Department of each participating hospital. Patients were eligible for the research group when the abdominal CT revealed >5 diverticula. Patients without diverticula, defined as 0 to ≤5 diverticula on abdominal CT, were included in the control group. The CTs were reviewed by radiologists who reported the diagnosis, the number of diverticula, the location of diverticula and, in the case of diverticulitis, the Hinchey classification. All patients eligible for this study were screened by the attending emergency physician, and informed consent was taken. The patient file and a patient questionnaire aimed to identify known risk factors for developing diverticula or acute diverticulitis. This questionnaire provided information on family history, patient diet, alcohol intake, packyears, physical exercise, stool production, and pattern and use of anti-coagulants, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or immunosuppressants. Blood samples were collected and the concentration of A1AT in serum was determined by immunoassay. Genotype analysis was performed, which revealed whether an individual had a normal genotype (PiMM), was a carrier of A1AT deficiency (PiM Heerlen, PiMS, PiMZ or PiMF) or had A1AT deficiency (PiSS, PiSZ and PiZZ).

**Study objective**

The objective was to determine the prevalence of A1AT deficiency (carriers) in patients with and without colonic diverticula.

**Laboratory analysis**

*DNA extraction, whole genome amplification*

DNA was extracted from 600 µl plasma or from 200 µl buffycoat. The Qiagen Mini Blood Kit (Qiagen Benelux BV, Venlo, The Netherlands) was used for the extraction of DNA. In some cases where the DNA concentration was too low to obtain the minimal coverage
criteria, whole genome amplification was performed on DNA extracted from a new plasma sample. The Qiagen REPLI-g FFPE kit (Qiagen Benelux BV) was used for whole genome amplification.

Sequencing
A targeted custom AmpliSeq panel was designed containing coding sequences for three known A1AT deficiency causing genes (SERPINA1, SERPINA3 and ELA2). In total 27 amplicons were designed covering 6.5 kb. The Ion Chef (Thermo Fisher Scientific, Waltham, Massachusetts, USA) was used to create a next-generation sequencing library for each sample. These libraries were pooled on an Ion chip and sequenced on an Ion S5 sequencer (Thermo Fisher Scientific). Using a hotspot file on TORRENT SUITE 5.4 or 5.8 software (Thermo Fisher Scientific) known variants responsible for A1AT deficiency were called.

Outcome measures
The primary study parameter was prevalence of A1AT deficiency or carriers in patients with and without colonic diverticula. Secondary study parameters were previous episodes of diverticulitis in patients with and without (carrier alleles for) A1AT deficiency and the number of diverticulitis-related hospital admissions and diverticulitis-related complications in patients with and without (carrier alleles for) A1AT deficiency.

Ethical considerations
The study was conducted in accordance with the principles of the Declaration of Fortaleza and ‘good clinical practice’ guidelines. The protocol (version 4, amendment 4, 7 December 2018) was approved by the Medical Research Ethics Committees of VU University Medical Center (MRECvUmc). Consent was also obtained from the participating centres. The patients were counselled and written informed consent was obtained from all patients if inclusion criteria were met.

Statistical analysis
Nominal and ordinal variables were described as numbers with proportions. Continuous variables were described as means with standard deviation (SD) or medians with interquartile range (IQR). Between group (cases vs controls) differences with respect to nominal and ordinal variables were analysed using the chi-squared test or the Fisher exact test where appropriate. Differences with respect to continuous variables were analysed using the independent samples t test or the Mann–Whitney U test depending on distribution. The strength of the association between exposure of A1AT pathology and the occurrence of diverticulosis was analysed by means of logistic regression analysis and expressed as an OR with 95% CI. Multivariable logistic regression analysis was used to correct this association for confounding effects. All secondary study parameters (except for A1AT concentration) were potential confounders and were selected as such in a forward selection procedure with a limit of 10% change in effect size using a basic logistic regression model with only exposure of A1AT pathology as independent variable and diverticulosis as dependent variable. The confounder with the largest change in effect size of the determinant (exposure of A1AT pathology) was included in the new model. The selection procedure was then repeated on the new model, using the remaining covariables. The procedure was stopped after none of the covariables changed the effect size by more than 10% or after reaching the maximum number of confounders defined as 10% of the number of patients with diverticulosis. Multiple imputation was used to deal with missing data. All secondary study parameters were analysed in patients with diverticula and compared between patients with and without the A1AT deficiency (carriers). Correction for multiple testing was done by using the Bonferroni correction. Differences with respect to continuous variables were analysed using the independent samples t test or Mann–Whitney U test depending on the distribution. Differences with regard to nominal or ordinal variables were analysed using the chi-squared test or Fisher exact test where appropriate.

STROBE guidelines for reporting will be followed [24]. All analyses were performed using SPSS, version 24.0 (SPSS Inc., Chicago, Illinois, USA).

Sample size calculation
It was assumed that there are at least 116 million carriers (PiMS and PiMZ) and 3.4 million deficiency allele combinations (PiSS, PiSZ and PiZZ) worldwide. The prevalence of A1AT deficiency carriers in Europe was calculated to be approximately 8% [16]. No previous information on the prevalence of A1AT deficiency (carriers) in patients with or without diverticula existed. Therefore, we could only speculate on the possible difference in prevalence between these two groups. To assess a 10% difference in prevalence at a significance level of 5% and a power of 80%, 115 patients per group were needed. Since the literature indicated that the prevalence of diverticulosis was around 50%, inclusion of cases and controls was expected to progress equally [25,26].
Data collection and monitoring

Data were collected from the medical records of the patients. Additional information was gathered using a questionnaire.

Results

Study design and population

The initial plan was to perform phenotype analyses because genotype analyses were (financially) not possible. However, during the inclusion period new developments in genotype analysis became available allowing us to perform genotype analysis. At that time, over 75% of the patients were already included, from whom we collected plasma samples.

A total of 258 patients were included; nine patients were excluded because of incomplete colon or free air on abdominal CT, making a reliable count of diverticula impossible. For analyses, 249 patients were included. Genotype analysis is possible from plasma samples but such samples contain limited amounts of DNA. For this reason, genotype analysis was not possible in 25 patients. Three patients withdrew informed consent after analyses were done, leaving a total of 221 patients (Fig. 1). The progression of inclusion of diverticulosis patients and controls did not proceed at the same pace. The final patient group with five or more diverticula comprised 144 (65.2%) patients and the control group 77 (34.8%) patients without at least five diverticula. The groups were comparable for age, gender and comorbidity such as cardiovascular diseases, diabetes mellitus and pulmonary pathology. Differences were observed for body mass index ($P = 0.012$). Possible risk factors extracted from patient records and questionnaires showed differences between the groups only for a positive family history of diverticulitis ($P = 0.019$) and use of NSAIDs ($P = 0.038$; Table 1). Patients were diagnosed with acute diverticulitis, appendicitis, cholecystitis, pancreatitis, obstructive ileus, malignancy, stomach or bowel perforation, ischaemia of the intestine, vascular disease, colitis, cardiac or pulmonary pathology, urological pathology, gastro-enteritis and obstipation.

Prevalence of A1AT deficiency (carriers)

In the overall population, two patients were diagnosed with A1AT deficiency (one with PiZZ and one with PiSS) and 24 patients were diagnosed as being a carrier of A1AT deficiency (Table S1). In the diverticulosis group, A1AT deficiency (or carrier) was found in 20 (13.9%) of 144 patients, whereas in the control group this was found in six (7.8%) of 77 patients. This difference was notable but not significant: crude OR of 1.9 (95% CI 0.732–4.974), $P = 0.186$. After adjustment for confounders (body mass index, use of NSAIDs, use of corticosteroids, nationality and fluid intake $\leq 1.5$ l/day) the adjusted OR for development of diverticula in patients with, or who are carriers for, A1AT deficiency was 1.5 (95% CI 0.5–4.0; $P = 0.466$; Table 2).

Subgroup analysis of patients with diverticula

Among the research group of 144 patients with diverticula, 64 patients were diagnosed with acute diverticulitis at first presentation. The number of patients with acute diverticulitis at presentation ($P = 0.957$), number of diverticula ($P = 0.705$) or location of diverticula ($P = 0.150$) were comparable among patients with and without A1AT deficiency (carriers) (Table 3a).

Subgroup analysis of patients with acute diverticulitis

Sixty-four of 221 patients were diagnosed with acute diverticulitis; nine of these 64 patients also had A1AT deficiency or were a carrier, and 55 of 64 patients were not. All parameters for disease severity were comparable between the two subgroups, such as Hinchey classification [uncomplicated diverticulitis (Hinchey 1a) vs complicated diverticulitis (Hinchey 1b, 2, 3)], C-reactive protein level and leukocyte count at presentation, days of hospital admission, whether a radiological or surgical intervention was needed, antibiotic treatment, need for intensive care unit admission, and 30-day mortality rate. A non-significant difference in 30-day mortality rate from acute diverticulitis between A1AT deficient patients (or carriers) and those without was observed: two (22.2%) of nine patients with A1AT deficiency $vs$ one (1.8%) of 55 without (Table 3b). No difference was found in the number of previous episodes of acute diverticulitis (Table 3b).

Discussion and conclusions

The hypothesis of the present study was that connective tissue diseases, in particular A1AT deficiency or being a carrier of this deficiency, contribute to the development of diverticula. The results showed a non-significant difference in the prevalence of A1AT between patients with and without diverticula, 13.9% $vs$ 7.8% respectively.

Because the prevalence of A1AT deficiency is low, approximately 0.24% in Europe, focus was on finding A1AT deficient carriers, which has a prevalence of 8% according to the literature [16]. We did anticipate that
the true prevalence of A1AT deficiency (carriers) may be underestimated. Indeed, we found a higher prevalence in the study population, being 11.8%. While assessing all other known risk factors for developing diverticulosis and diverticulitis the present study gives a good impression of the true influence of connective tissue disease related A1AT deficiency or carrier in the aetiology of diverticulosis. The current literature often mentions that connective tissue diseases play a role in diverticulitis; however, most of the information is based on old data, case reports and twin studies [27–29]. The results of the subgroup of patients with acute diverticulitis were notable. The deficient group was non-significantly more often diagnosed with complicated diverticulitis (≥Hinchey 1b) (44.4% vs 29.1%) than the non-deficient group. Thirty-day mortality was non-significantly higher in the deficient group (22.2% vs 1.8% without A1AT deficiency; Table 3b). Other than before the start of this study, A1AT deficiency may play a role in disease severity (course of disease) rather than development of diverticulitis, or both.

A limitation of this study was the fact that our laboratory analysis was changed during the study from phenotype analysis to genotype analysis. Although genotype analysis is a better method for diagnosing a patient with A1AT deficiency (or being a carrier), plasma samples – which were being collected at that point – contained limited amounts of DNA. For this reason, genotype analysis was not possible in 25 patients. Another limitation is that the literature indicates that the prevalence of diverticulosis in symptomatic patients is around 50% based on CT colonography [25,26]. Based on these data, inclusion of diverticula cases and controls was expected to progress equally. However, in the ALADDIN study, 144 (65.2%) patients were assigned to the research group and 78 (34.8%) patients to the control group, screened between 2017 and 2019 by abdominal CT. A possible explanation for the asymmetric distribution of cases and controls in the ALADDIN study would be that the study involved a population with acute abdominal pain instead of symptomatic non-acute patients. This may have caused the study to be under-powered for the hypothesis. Moreover, we did not perform a separate sample size calculation for the subgroup analysis of diverticulitis patients only, but the subgroup analysis itself was pre-specified in the protocol.

At the time this study was conducted little or no evidence was available in the literature on the role of connective tissue diseases in the development of diverticula. Recently, a genome-wide association analysis of diverticular disease and connective tissue pathological mechanisms has been published [30]. Regarding the polygenetic risk signature of diverticular disease, an overlap with syndromic neuromuscular, connective tissue and morphogenesis disorders and previous findings was observed. Manifestation of diverticulitis may be

Figure 1 The ALADDIN study flowchart comprising the study population, including inclusion and exclusion criteria.
Table 1 Baseline characteristics including possible risk factors for diverticulosis or diverticulitis based on the literature.

|                                | All patients (N = 221) | Diverticula group (N = 144) | Control group (N = 77) | P value |
|--------------------------------|------------------------|-----------------------------|------------------------|---------|
| Age, years, mean (SD)          | 72.28 (7.94)           | 72.88 (8.37)                | 71.16 (6.96)           | 0.105   |
| Female gender, n (%)           | 128 (57.9)             | 82 (56.9)                   | 46 (59.7)              | 0.688   |
| Nationality, Dutch, n (%)      | 213 (98.2)             | 142 (99.3)                  | 71 (95.9)              | 0.116   |
| BMI (kg/m²), mean (SD)         | 26.78 (4.92)           | 27.38 (5.07)                | 25.64 (4.44)           | 0.012   |
| Comorbidity, n (%)             |                        |                             |                        |         |
| Myocardial infarction          | 26 (11.8)              | 15 (10.4)                   | 11 (14.3)              | 0.395   |
| Cerebral ischaemia             | 20 (9.0)               | 11 (7.6)                    | 9 (11.7)               | 0.317   |
| Hypertension                   | 79 (35.7)              | 55 (38.2)                   | 24 (31.2)              | 0.299   |
| Heart failure†                 | 10 (4.5)               | 7 (4.9)                     | 3 (3.9)                | 1.000   |
| Peripheral arterial disease    | 16 (7.2)               | 11 (7.6)                    | 5 (6.5)                | 0.754   |
| Diabetes mellitus              | 32 (14.5)              | 20 (13.9)                   | 12 (15.6)              | 0.733   |
| Renal failure†                 | 8 (3.6)                | 6 (4.2)                     | 2 (2.6)                | 0.717   |
| Pulmonary diseases             | 56 (25.3)              | 39 (27.1)                   | 17 (22.1)              | 0.415   |
| Connective tissue disease      | 32 (14.5)              | 22 (15.3)                   | 10 (13.0)              | 0.645   |
| Family members with diverticulitis, n (%)§ | 19 (9.1) | 17 (12.5) | 2 (2.7) | 0.019 |
| Fibre diet, n (%)*¶           | 109 (50.9)             | 67 (47.9)                   | 42 (56.8)              | 0.215   |
| Fluid intake ≤ 1.5 l/day, n (%)** | 55 (25.6) | 30 (21.4) | 25 (33.3) | 0.057 |
| Coffee intake, n (%)†**        | 206 (95.8)             | 133 (95.0)                  | 73 (97.3)              | 0.501   |
| Alcohol intake, n (%)††        | 149 (68.3)             | 98 (68.5)                   | 51 (68.0)              | 0.936   |
| Current smoker, n (%)‡‡        | 34 (15.5)              | 21 (14.7)                   | 13 (17.1)              | 0.638   |
| Packyears, median (IQR)†††     | 6 (0–26)               | 7 (0–26)                    | 4 (0–27)               | 0.625   |
| Physical exercise> 30 min/day, n (%)§§ | 56 (26.0) | 41 (29.3) | 15 (20.0) | 0.139 |
| Daily stool production, n (%)§ | 181 (86.6)             | 118 (86.1)                  | 63 (87.5)              | 0.783   |
| Changes in defaecation pattern, n (%)§§§ | 60 (28.8) | 40 (29.6) | 20 (27.4) | 0.734 |
| Use of anticoagulants, n (%)¶¶ | 94 (42.5)              | 63 (43.8)                   | 31 (40.3)              | 0.617   |
| Use of NSAIDs, n (%)***        | 46 (21.7)              | 24 (17.4)                   | 22 (29.7)              | 0.038   |
| Use of immunosuppressants, n (%)††‖‖ | 13 (5.9) | 10 (6.9) | 3 (3.9) | 0.550 |
| Average no. of diverticula      | 6–10                   | 11–15                       | 0–5                    | –       |

BMI, body mass index; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.
Bold indicates statistically significant values.
*According to the Dutch Nutrition Centre (Voedingscentrum).
†Fisher’s exact test.
‡Eight missing.
¶Seven missing.
§Twelve missing.
**Six missing.
††Three missing.
‡‡Two missing.
§§Thirteen missing.
¶¶Acetylsalicylic acid, vitamin-K antagonists or heparin.
***Nine missing.
††‖One missing.

Table 2 Crude odds ratio and adjusted odds ratio with P values for A1AT deficiency (carrier) as a risk factor for diverticulosis, acute diverticulitis and a more severe course of acute diverticulitis.

|                                | All patients (N = 221) | Diverticula group (N = 144) | Control group (N = 77) | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted P value |
|--------------------------------|------------------------|-----------------------------|------------------------|-------------------|---------------------|-----------------|
| A1AT deficiency (carriers)     | 26 (11.8)              | 20 (13.9)                   | 6 (7.8)                | 1.909 (0.732–4.974) | 1.455 (0.532–3.981) | 0.466           |

A1AT, alpha-1-antitrypsin.
triggered by epithelial dysfunction of an altered colon anatomy [30]. This is in line with our hypothesis that changes in anatomy, specifically the connective tissue, play a role in the development of diverticula and possibly are involved in acute diverticulitis.

In this study, we found no convincing evidence that A1AT deficiency (or carrier status) plays a role in the aetiology of diverticulitis, although deficient patients and carriers had a higher mortality when experiencing diverticulitis. The formation of diverticula and the development of acute diverticulitis seem to be multifactorial. We believe that our hypothesis cannot be rejected permanently or firmly based on the observed but non-significant differences in prevalence. Patients who have (or are carriers for) A1AT deficiency showed a trend towards more diverticula and, when diagnosed with acute diverticulitis, had a higher mortality.

### Table 3

(a) Baseline characteristics for patients with diverticulosis or diverticulitis comparing patients with and without A1AT deficiency (carriers); (b) baseline characteristics for patients with acute diverticulitis comparing patients with and without A1AT deficiency (carriers).

| (a) Diverticula group (N = 144) | With A1AT carrier/deficiency (N = 20) | Without A1AT carrier/deficiency (N = 124) | P value† |
|--------------------------------|--------------------------------------|------------------------------------------|---------|
| **Number of diverticula, n (%)*** |                                     |                                          |         |
| 6–10 diverticula               | 25 (17.7)                            | 4 (20.0)                                 | 0.705   |
| 11–15 diverticula              | 22 (15.6)                            | 3 (15.0)                                 | 19 (15.7)|
| 16–20 diverticula              | 18 (12.8)                            | 3 (15.0)                                 | 15 (12.4)|
| 21–25 diverticula              | 17 (12.1)                            | 4 (20.0)                                 | 13 (10.7)|
| > 25 diverticula               | 59 (41.8)                            | 6 (30.0)                                 | 53 (43.8)|
| **Location of diverticula, n (%)*** |                                     |                                          |         |
| Left                           | 95 (67.4)                            | 17 (85.0)                                | 78 (64.5)| 0.150  |
| Right                          | 0                                    | 0                                        | 0        |
| Both                           | 35 (24.8)                            | 3 (15.0)                                 | 32 (26.4)|
| Pan                            | 11 (7.8)                             | 0                                        | 11 (9.1) |
| **Diverticulitis at presentation, n (%)** |                                     |                                          | 0.957   |
|                                | 64 (44.8)                            | 9 (45.0)                                 | 55 (44.4)|

| (b) Patients with acute diverticulitis (N = 64) | With A1AT carrier/deficiency (N = 9) | Without A1AT carrier/deficiency (N = 55) | P value† |
|-----------------------------------------------|--------------------------------------|------------------------------------------|---------|
| **Previous episode of acute diverticulitis, n (%)** |                                       |                                          |         |
| 1 (uncomplicated)                             | 44 (68.8)                            | 5 (55.6)                                 | 39 (70.9)| 0.443  |
| ≥ 1b (complicated)                            | 20 (31.3)                            | 4 (44.4)                                 | 16 (29.1)|
| **C-reactive protein (CRP) at presentation, median (IQR)** |                                       |                                          |         |
| 108 (54–188)                                 | 95 (55–210)                          | 108 (54–188)                             | 0.796   |
| **White blood cell count (WBC), leukocytes at presentation, mean (SD)** |                                       |                                          |         |
| 13.7 (7.2)                                   | 15.1 (5.0)                           | 15.5 (7.5)                               | 0.571   |
| **Days of admission, median (IQR)** |                                       |                                          |         |
| 3 (0–7)                                      | 1 (0–12)                             | 3 (0–7)                                  | 1.000   |
| **Intervention needed, n (%)**               |                                       |                                          |         |
| 3 (11.1)                                     | 1 (11.1)                             | 6 (11.1)                                 | 1.000   |
| **Received antibiotic treatment, n (%)**      |                                       |                                          |         |
| 29 (45.3)                                    | 3 (33.3)                             | 26 (47.3)                                | 0.494   |
| **Emergency surgery, n (%)**                 |                                       |                                          |         |
| 9 (14.1)                                     | 1 (11.1)                             | 8 (14.5)                                 | 1.000   |
| **ICU admission, n (%)**                     |                                       |                                          |         |
| 3 (4.7)                                      | 0 (0)                                | 3 (5.5)                                  | 1.000   |
| **30-day mortality, n (%)**                  |                                       |                                          | 0.0495  |
| 3 (4.7)                                      | 2 (22.2)                             | 1 (1.8)                                  | 0.111   |
| **Concentration A1AT, mean (SD)**            |                                       |                                          |         |
| 2.17 (0.754)                                 | 1.80 (0.67)                          | 2.23 (0.75)                              |         |

A1AT, alpha-1-antitrypsin; ICU, intensive care unit; IQR, interquartile range.

Bold indicates statistically significant values.

*Fisher’s Exact test.
†Two missing.
‡Corrected for multiple testing (Bonferroni), significance level 0.05/11 = 0.0045.
§One missing.

S. J. Rottier et al. Alpha-1-antitrypsin deficiency and colonic diverticula
diverticulitis, appeared to have a more severe course of diverticulitis compared to the patients with a normal type of A1AT. Foremost, these results indicate that further research is justified as a trend but no convincing evidence was found that A1AT deficiency plays a role in the aetiology of diverticulitis. This may be due to the fact that diverticulitis is a multifactorial disease and larger numbers may be needed to explore the role of A1AT deficiency amongst other contributing factors. Future studies not only may focus on A1AT deficiency alone but may extend to multiple connective tissue diseases.

Acknowledgements

W.M. van Vuuren, pre-analysis clinical chemical hematicological laboratory Tergooi, W.K.C. Koot-Peet, pre-analysis clinical chemical hematicological laboratory Tergooi, L. Hoogendoorn, clinical chemical laboratory NWZ, and I. van der Hulst, clinical chemical laboratory NWZ.

Conflicts of interest

Drs S.J. Rottier, Drs L.C. Dreuning, Dr J. van Pelt, Dr A.A.W. van Geloven, Drs X.Y.D. Beele, Drs P.M. Huisman, Drs W.Y. Deurholt, Drs C.A. Rottier, K. van Leeuwen, M. de Boer, G. van Mierlo, Professor M.A. Boermeeestert, Dr W.H. Schreurs critically revised the manuscript for important intellectual content. Drs S.J. Rottier, Drs L.C. Dreuning, Dr J. van Pelt, Dr A.A.W. van Geloven, Drs X.Y.D. Beele, Drs P.M. Huisman, Drs W.Y. Deurholt, Drs C.A. Rottier, K. van Leeuwen, M. de Boer, G. van Mierlo, Professor M.A. Boermeester, Dr W.H. Schreurs gave final approval of the version to be published and are accountable for all aspects of the work.

References

1 Sharara AI, El-Halabi MM, Mansour NM et al. Alcohol consumption is a risk factor for colonic diverticulosis. J Clin Gastroenterol 2013; 47: 420–5.
2 Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit times, and its role in the causation of disease. Lancet 1972; 2: 1408–12.
3 Comstock SS, Lewis MM, Pathak DR, Hortos K, Kovan B, Fenton JJ. Cross-sectional analysis of obesity and serum analytes in males identifies sRAGE as a novel biomarker inversely associated with diverticulosis. PLoS One 2014; 9: e95232.
4 Granlund J, Svensson T, Olen O et al. The genetic influence on diverticular disease – a twin study. Aliment Pharmacol Ther 2012; 35: 1103–7.
5 Hjern F, Mahmood MW, Abraham-Nordling M, Wolk A, Hakansson N. Cohort study of corticosteroid use and risk of hospital admission for diverticular disease. Br J Surg 2015; 102: 119–24.
6 Hjern F, Wolk A, Hakansson N. Smoking and the risk of diverticular disease in women. Br J Surg 2011; 98: 997–1002.
7 Painter NS. Diverticular disease of the colon. Br Med J 1968; 8: 475–9.
8 Daniels L, Philipszoon LE, Boermeester MA. A hypothesis: important role for gut microbiota in the etiopathogenesis of diverticular disease. Dis Colon Rectum 2014; 57: 539–43.
9 Rottier SJ, de Jonge J, Dreuning LC et al. Prevalence of alpha-1-antitrypsin deficiency carriers in a population with and without colonic diverticula. A multicentre prospective case–control study: the ALADDIN study. Int J Colorectal Dis 2019; 34: 933–8.
10 Szojda MM, Cuesta MA, Mulder CM, Felt-Bersma RJ. Review article: Management of diverticulitis. Aliment Pharmacol Ther 2007; 26(Suppl 2): 67–76.
11 Watters DA, Smith AN, Eastwood MA, Anderson KC, Elton RA, Mugerwa JW. Mechanical properties of the colon: comparison of the features of the African and European colon in vitro. Gut 1985; 26: 384–92.
12 Weiss L, Eastwood MA, Wess TJ, Busuttil A, Miller A. Cross linking of collagen is increased in colonic diverticulosis. Gut 1995; 37: 91–4.
13 Bode MK, Karttunen TJ, Makela J, Risteli L, Risteli J. Type I and III collagens in human colon cancer and diverticulosis. Scand J Gastroenterol 2000; 35: 747–52.
14 Rosemar A, Ivarsson ML, Borjesson L, Holmdahl L. Increased concentration of tissue-degrading matrix metalloproteinases and their inhibitor in complicated diverticular disease. *Scand J Gastroenterol* 2007; 42: 215–20.

15 Wedel T, Barrenschee M, Lange C, Cossais F, Bottner M. Morphologic basis for developing diverticular disease, diverticulitis, and diverticular bleeding. *Viszeralmedizin* 2015; 31: 76–82.

16 de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest* 2002; 122: 1818–29.

17 Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency—a model for conformational diseases. *N Engl J Med* 2002; 346: 45–53.

18 Stoller JK, Aboussouan LS. A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2012; 185: 246–59.

19 Suki B, Bates JH. Extracellular matrix mechanics in lung parenchymal diseases. *Respir Physiol Neurobiol* 2008; 163: 33–43.

20 Nagase H, Woessner JF Jr. Matrix metalloproteinases. *J Biol Chem* 1999; 274: 21491–4.

21 Ohnishi K, Takagi M, Kurokawa Y, Satomi S, Konttinen YT. Matrix metalloproteinase-mediated extracellular matrix protein degradation in human pulmonary emphysema. *Lab Invest* 1998; 78: 1077–87.

22 McAloon CJ, Wood AM, Gough SC, Stockley RA. Matrix metalloprotease polymorphisms are associated with gas transfer in alpha 1 antitrypsin deficiency. *Thor Adv Respir Dis* 2009; 3: 23–30.

23 Tanash HA, Ekstrom M, Wagner P, Piitulainen E. Cause-specific mortality in individuals with severe alpha 1-antitrypsin deficiency in comparison with the general population in Sweden. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1663–9.

24 von Elm E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–7.

25 De Cecco CN, Ciolli M, Annibale B *et al*. Prevalence and distribution of colonic diverticula assessed with CT colonography (CTC). *Eur Radiol* 2016; 26: 639–45.

26 Golder M, Ster IC, Babu P, Sharma A, Bayat M, Farah A. Demographic determinants of risk, colon distribution and density scores of diverticular disease. *World J Gastroenterol* 2011; 17: 1009–17.

27 Borsch G, Pusch H, Borger G. Perforated sigmoid diverticulitis in identical twins. *Dig Dis Sci* 1986; 31: 558.

28 Claassen AT, Mourad-Baars PE, Mearin ML, Hilhorst-Hofstee Y, Gerritsen van der Hoop A. Two siblings below the age of 20 years with diverticular disease. *Int J Colorectal Dis* 2006; 21: 190–1.

29 Frieden JH, Morgenstern L. Sigmoid diverticulitis in identical twins. *Dig Dis Sci* 1985; 30: 182–3.

30 Schafmayer C, Harrison JW, Buch S *et al*. Genome-wide association analysis of diverticular disease points towards neuromuscular, connective tissue and epithelial pathomechanisms. *Gut* 2019; 68: 854–65.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Histogram with additional information on number of diverticula in the control and diverticula groups.

**Table S1.** Additional information on patients with A1AT deficiency (or carriers).