

BMJ Open Perforated appendicitis in patients with schizophrenia: a retrospective cohort study

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ABSTRACT

Objective Altered pain sensitivity may affect the outcome of appendicitis in patients with schizophrenia. We aimed to compare the prevalence of perforation in appendicitis between patients with and without schizophrenia.

Design Retrospective cohort study with random matching.

Setting A single tertiary medical centre in Japan.

Participants From 1985 to 2013, 1821 cases of appendicitis requiring appendectomy were collected. Patients with schizophrenia and a cohort of randomly selected control subjects without schizophrenia who underwent appendectomy were identified.

Primary and secondary outcome measures The primary outcome was the rate of perforated appendicitis in patients with and without schizophrenia. Secondary outcome was the odds of perforated appendicitis by different clinical factors.

Results 62 patients with schizophrenia and randomly sampled 200 non-schizophrenic patients were compared. The prevalence of perforation was 53% in patients with schizophrenia versus 17% in controls ($p<0.0001$). The adjusted OR for perforation were 4.87 (95% CI: 2.33 to 10.2) for schizophrenia, 3.35 (95% CI 1.51 to 7.45) for age >55 years and 2.18 (95% CI: 1.12 to 4.27) for delayed presentation.

Conclusion Appendiceal perforation was more frequent in patients with schizophrenia than controls, which may be partly attributable to delayed presentation and altered responses to pain.

INTRODUCTION

Early diagnosis of appendicitis is necessary in order to prevent increased surgical morbidity and mortality due to abscess and perforation.¹ The mortality of appendicitis has been estimated at 2.4 per million and the morbidity has been estimated at 7.7–17.8 per million.^{2,3}

Schizophrenia is a psychiatric disorder consisting of chronic or recurrent psychosis that affects 15 per 100 000 persons. The median lifetime morbidity risk for schizophrenia is 7.2 per 1000 persons.⁴ Patients with schizophrenia have often been noted to have decreased perception of pain with altered expression of the emotional response to pain. Pain insensitivity (hypoalgesia) has been described in psychotic disorders since

Strengths and limitations of this study

- This is one of the few retrospective cohort studies with random matching using real-world clinical data to evaluate ruptured appendicitis and its complications among patients with schizophrenia.
- Detailed clinical parameters correlated with surgical outcome during three decades of clinical practice allow us to address the magnitude of schizophrenia on excess adverse outcome independent of other risk factors that may vary over time.
- The retrospective collection of clinical factors is subject to recall bias and other biases.
- We lack data concerning potential differences in the time course of hospital evaluation, and whether the diagnosis of schizophrenia impeded progression of the diagnostic process.

the early 20th century.^{5,6} Kraepelin noted that patients often become less sensitive to body discomfort: “They endure uncomfortable positions, pricks of needles, injuries, without thinking much of it.”⁶ Bleuler observed unusual self-mutilation such as eye enucleation and autocastration and noted the ‘complete analgesia’ in patients with schizophrenia.⁵ Prior studies indicated diagnostic and surgical delay of somatic problems may often be encountered among patients with schizophrenia.^{7,8} Patients with schizophrenia who require appendectomy have a high rate of perforation and other adverse outcomes.⁹ Tsay and his colleagues reported that the rate of appendiceal perforation was 46.7% among schizophrenic cohort and 25.1% among patients without major psychiatric disorders, suggesting that schizophrenia was associated with a 2.83 times higher risk of having a ruptured appendix.¹⁰ Cooke *et al* reported a 66% perforation rate in a case series of appendicitis in patients with schizophrenia.⁹ Smoking and comorbid conditions such as diabetes and obesity are commonly seen in schizophrenia, and may partly explain the higher rates of appendiceal rupture. The increased rate of complications



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in schizophrenia has been consistent, but the contributions of pain insensitivity and delayed access to medical care have not been defined.

This retrospective cohort study was designed to examine the clinical characteristics of appendicitis in schizophrenic subjects, and to compare the rate of complications to patients without schizophrenia.

METHODS

Study subjects

All patients ≥ 18 years old who had an appendectomy for suspected appendicitis from 1985 to 2013 were collected retrospectively from the record system at Okinawa Chubu Hospital, a tertiary medical centre in Japan. We stratified patients as to whether schizophrenia was present, defined as a diagnosis rendered by a psychiatrist with the confirmation an antipsychotic medication prescription. In no cases were antipsychotic medications prescribed for any control subjects. The diagnosis of schizophrenia corresponded to DSM-4 text revision criteria. Sixty-two patients with schizophrenia and 1759 control subjects without schizophrenia who underwent appendectomy during the observation period were identified. Two hundred patients were randomly selected as controls. This study was approved by the Institutional Ethics Committee of Okinawa Chubu Hospital.

Diagnosis of appendicitis and clinical characteristics

Data collected included the presenting history and physical examination findings, and the results of CT or ultrasound studies performed prior to surgery. Most appendectomies were performed as open surgery and only a few patients underwent laparoscopic intervention in our cohort. Appendicitis was confirmed by surgical and pathological findings, and the presence of rupture or abscess was noted. Perforated appendicitis was defined either intraoperatively or postoperatively, based on pathological findings. Patient characteristics were recorded including age, gender, smoking, body mass index (kg/m^2), history of diabetes and date of appendectomy. Tobacco use was reported by patients and was dichotomised as current versus former/never. Diabetes was self-reported. Clinical characteristics of appendicitis that were collected included abdominal pain, nausea and vomiting. The duration of abdominal symptoms at the time of emergency department (ED) presentation was categorised as either 2 days or longer versus less than 2 days; the duration from ED presentation to operating room was categorised as either 12 hours or longer versus less than 12 hours; vital signs including temperature of 38°C or higher and tachycardia >100 beats per minute; signs of peritoneal irritation including guarding and rebound tenderness; leucocytosis (white blood cell count $10 \times 10^9/\text{L}$). Ultrasound or CT findings were recorded, with note of whether appendicitis was reported to be likely. Medication use was ascertained, including antipsychotic drugs (clozapine, olanzapine, risperidone,

chlorpromazine hydrochloride, levomepromazine, haloperidol, perospirone and zotepine), benzodiazepine, serotonin selective reuptake inhibitors, tricyclic antidepressants, anticholinergics, corticosteroids and non-steroidal anti-inflammatory drugs.

Statistical analysis

Sample size calculations were based on a 30% frequency of perforation in appendicitis in general population and a 66% frequency of perforated appendicitis in schizophrenia.¹⁰ Detecting differences of this magnitude with 80% or 90% power yielded sample sizes of 29 and 39 patients per group. Controls were selected randomly from all non-schizophrenic patients, using a table of random numbers. Continuous variables were compared using Student's t-test and categorical variable by a two-sided Fisher's exact test, as appropriate; all tests were performed at a 5% level of significance.

Logistic regression was performed to assess the OR for perforation between schizophrenic and non-schizophrenic patients, controlling for age, gender, body mass index, diabetes, smoking and time of presentation. In sensitivity analysis, a second cohort of age-matched controls was selected from the base non-schizophrenic population, with three controls for each schizophrenic subject, and a conditional logistic regression was performed.

All analyses were performed using R with no additional packages installed (R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>), using the EZR statistical interface, V.2.13.0. The same analysis was replicated using STATA V.14.2.

RESULTS

Sixty-two cases of appendicitis in patients with schizophrenia were detected, and these cases were compared with 200 controls. Among patients with schizophrenia, the mean age was 43.5 years and 40% were female; in controls, mean age was 40.2 years and 46% were female ($p > 0.15$ for both comparisons). Baseline characteristics of both groups are shown in [table 1](#). Compared with controls, the patients with schizophrenia were more likely to be current smokers and have diabetes. Most patients with schizophrenia reported abdominal pain. Consistent with their underlying psychiatric diagnosis, the use of neuroleptics, anxiolytics and anticholinergic drugs was higher in the schizophrenic group, but the use of antidepressants was infrequent in both groups.

Clinical characteristics during the ED presentation are provided in [table 2](#). Compared with controls, patients with schizophrenia were more likely to be febrile and tachycardic, and had a higher frequency of guarding on abdominal examination. Rebound tenderness was common in both groups (83% vs 73%, $p = 0.16$). Leucocytosis did not differ between groups. Compared with controls, patients with schizophrenia were significantly more likely to report that the duration of symptoms was >48 hours prior to ED

Table 1 Baseline characteristics of patients with appendicitis, by presence or absence of schizophrenia

	Schizophrenia (n=62)		Controls (n=200)		p Value
	n	%	n	%	
Age, mean (SD)	43.5	11.6	40.2	17.1	0.17
Female	25	40	92	46	0.48
BMI >25	21	38	52	27	0.13
Current tobacco	45	74	92	46	0.0002
Diabetes	8	13	6	3	0.006
Medications					
Neuroleptic	62	100	0	0	<0.0001
Benzodiazepine	38	73	4	2	<0.0001
Anticholinergic	45	85	0	0	<0.0001
SSRI	0	0	1	1	1
TCA	2	4	1	1	0.11
NSAID	2	4	3	2	0.28
Glucocorticoids	0	0	4	2	0.58

BMI, body mass index; SSRI, selective serotonin reuptake inhibitors; NSAID, non-steroidal anti-inflammatory drugs; TCA, tricyclic antidepressants.

presentation (47% vs 25%, $p=0.002$). Time from ED to operating room was not different between groups (31% vs 24%, $p=0.3$).

The unadjusted odds of having perforated appendicitis were 2.7 times higher in patients aged 55 or older, 2.99 times higher for delayed presentation and 5.56 times higher in patients with schizophrenia (table 3). Schizophrenia remained the strongest risk factor for perforation, even after adjustment for age, gender, body mass

Table 2 Preoperative findings in patients with and without schizophrenia

	Schizophrenia	Controls	p Value
	N (%)	N (%)	
Temp >38.0°C	25 (40)	38 (19)	0.001
Abdominal pain	61 (98)	199 (100)	0.24
Nausea/vomiting	32 (65)	129 (70)	0.602
Pulse >100/min	37 (61)	31 (16)	<0.0001
Rebound tenderness	48 (83)	127 (73)	0.16
Guarding	35 (65)	37 (32)	0.0001
WBC >10 000/ μ L	48 (77)	152 (77)	1.0
Delayed presentation*	28 (47)	50 (25)	0.002
Delayed ED to OR†	18 (31)	45 (24)	0.3

*Delayed presentation defined as more than 48 hours of symptoms prior to presentation for care.

†Delayed ED to OR defined as >12 hours of ED stay prior to appendectomy.

ED, emergency department; OR, operating room; Temp, temperature; WBC, white blood cell.

index, diabetes or tobacco use (OR=5.42, 95% CI 2.66, 11.1). However, adjusting for delayed presentation in our model attenuated the association between schizophrenia and perforation (OR=4.87, 95% CI 2.33 to 10.2). Among patients with schizophrenia, the odds of perforation did not differ between early versus delayed presentation (53% vs 57%, $p=0.8$). Once diagnosed, patients with schizophrenia were more likely to have longer hospital lengths of stay, more postoperative complications and unfavourable histopathology (table 4).

The rate of ruptured appendicitis did not differ before and after the year 2000 (58% vs 52%, $p=0.79$ in schizophrenia, 19% vs 12%, $p=0.7$ in controls), when CT scan for the diagnosis of appendicitis became more readily available, with better image quality.

Sensitivity analysis

In our sensitivity analysis using a cohort of matched controls and adjusting for the same demographic and clinical factors (including time of presentation), age >55 was no longer a risk for perforation (OR=0.77, 95% CI 0.14, 4.22). However, schizophrenia remained a significant risk factor (OR=2.96, 95% CI 1.39, 6.27) as well as delayed presentation (OR=4.46, 95% CI 2.30, 8.64).

DISCUSSION

This retrospective cohort study described the features of appendicitis in patients with schizophrenia and demonstrated that patients with schizophrenia had substantially greater odds of having perforation. Increased risk at the time of operation was independent of known risk factors such as age, smoking or diabetes, compared with non-schizophrenics. Most patients with schizophrenia reported classic abdominal symptoms. This study provided insights into the poor outcomes experienced by this vulnerable patient group.

Contrary to the notion that patients with schizophrenia are insensitive to pain and somatic sensation,^{11 12} the present study demonstrated that most patients with schizophrenia presented with classic symptoms of appendicitis including abdominal pain as reported previously.⁹ In our study, some clinical signs such as fever, tachycardia and abdominal guarding were more pronounced in schizophrenics. About half (47%) of the patients with schizophrenia took more than 2 days to access hospital care after the onset of abdominal symptoms, so delay in seeking medical attention may partly explain the discrepant clinical presentation and higher incidence of perforated appendicitis in schizophrenia.

Diabetes and tobacco use have been associated with increased risk of perforation in appendicitis.^{13–15} Our findings are concordant with other studies in which patients with schizophrenia are more likely to be overweight, diabetic and less likely to adhere to a healthy lifestyle.¹⁶ Bushe reported the prevalence of diabetes was approximately 15% in a sample of patients with schizophrenia.¹⁷ In another study, 65%–79% of patients with

Table 3 Odds of perforated appendicitis by clinical factors

Characteristics	Unadjusted OR (95% CI)	Fully adjusted OR (95% CI)*
Age>55	2.7 (1.42 to 5.23)	3.35 (1.51 to 7.45)
Female sex	1.09 (0.63 to 1.91)	1.16 (0.60 to 2.23)
Diabetes mellitus	2.30 (0.77 to 6.89)	0.96 (0.27 to 3.39)
Body mass index >25	1.57 (0.87 to 2.72)	1.41 (0.71 to 2.81)
Current smoker	1.54 (0.87 to 2.72)	1.23 (0.62 to 2.46)
Schizophrenia	5.56 (2.99 to 10.3)	4.87 (2.33 to 10.2)
Time of presentation		
>48 hours	2.99 (1.66 to 5.63)	2.18 (1.12 to 4.27)

*Age, gender, diabetes, smoking, body mass index, schizophrenia and time of presentation.

schizophrenia were reported to be smokers.¹⁸ Despite this, our data showed that adjustment for traditional risk factors did not attenuate the association of schizophrenia with increased appendiceal rupture. Schizophrenia was more strongly associated with ruptured appendicitis than any other variable we evaluated.

The increased risk of perforation in schizophrenia was attenuated when the model was adjusted for delayed presentation, suggesting that patients with schizophrenia may be systematically less likely to seek medical care in response to abdominal pain. Delayed presentation has been associated with the risk of perforation in other populations.¹⁹ Nearly all of our patients with schizophrenia reported abdominal pain, contradicting the notion that they do not experience pain. However, patients with schizophrenia may have abnormal perception and reporting of pain, which may be related to

medications or the underlying psychiatric disorder.²⁰ Delay in seeking medical attention may be partially attributable to altered pain sensitivity in schizophrenia. Our data contrast with those of Marchand, who reported that 37% of schizophrenia patients with appendicitis reported no pain.²¹ Lack of insurance and financial restrictions are minimised under the universal healthcare system in Japan, which confers support for living costs and medical expenditures for patients diagnosed with schizophrenia. However, our data do not permit us to speculate on non-financial factors such as perceptions of stigma in the healthcare setting.

Once hospitalised, patients with schizophrenia with appendicitis had more unfavourable surgical findings, and had poorer outcomes with increased complications. Our data are consistent with those of Daumit *et al*, who noted that patients with schizophrenia have a greater than twofold risk of major avoidable in-hospital complications.²² Patients with schizophrenia suffered from more medical complications and longer lengths of stay, partially reflecting later presentation with more advanced inflammatory deterioration of the appendix and surrounding tissues. Regardless of the timing of presentation, however, our data indicate that there is still substantial excess risk of perforation associated with schizophrenia. We cannot rule out the possibility that the pathophysiology of appendicitis may be different in patients with schizophrenia, due to alterations in the microbiome or altered inflammatory responses.^{11 12}

Our data do not permit us to draw conclusions about the associations between antipsychotic medication use, or severity of schizophrenia, and appendiceal perforation. Patients with schizophrenia tended to have more severe psychiatric symptoms in the inpatient setting, and often required increased medications. However, our results show that the rate of perforation did not differ between hospitalised and non-hospitalised patients with schizophrenia (50% vs 71% $p=0.11$), suggesting that schizophrenia itself, rather than the medications for schizophrenia, is a risk factor for perforated appendicitis.

There are several strengths in this study. First, this is one of a few cohort studies that has evaluated ruptured

Table 4 Characteristics of perforated appendicitis and hospitalisation, by presence or absence of schizophrenia

	Schizophrenia Controls		p Value
	N (%)	N (%)	
Perforation	33 (53)	34 (17)	<0.0001
Hospital length of stay >7 days	43 (69)	72 (36)	<0.0001
Death	0 (0)	1 (1)	1
Wound healing by secondary intention	35 (56)	44 (22)	<0.0001
Wound infection	0 (0)	6 (3)	0.34
Appendiceal tear at operation	2 (3)	8 (4)	1
Suppurative ascites	1 (1)	2 (1)	0.56
Intra-abdominal abscess	19 (31)	14 (7)	<0.0001
Bacteraemia/sepsis	5 (8)	5 (3)	0.06
Reoperation	3 (5)	0 (0)	0.01
Respiratory arrest	1 (2)	1 (1)	0.42
Gangrenous or necrotic appendicitis	27 (43)	29 (15)	<0.0001

appendicitis and its complications among patients with schizophrenia. Second, detailed clinical parameters with surgical outcome during three decades of clinical practice allow us to address the magnitude of schizophrenia on excess adverse outcome independent of other risk factors that may vary over time.

Several limitations merit discussion. The retrospective collection of risk factors is subject to recall bias and other biases. However, our data showed proportions of current smokers and diabetes in schizophrenia that were similar to other studies. We did not have data concerning potential differences in dietary habits, the time course of hospital evaluation, and whether the diagnosis of schizophrenia impeded progression of the diagnostic process. We also lacked sufficient data to define the effects of antipsychotics, antidepressants or benzodiazepines and other medications on pain sensitivity.

In conclusion, patients with schizophrenia are at high risk for perforation and other complications of appendicitis, due in part to delayed presentation with more advanced inflammation. Further work may reveal strategies to improve outcomes in these vulnerable patients.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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