Diploma Thesis

EPIDEMIOLOGICAL ANALYSIS OF APPENDECTOMY SPECIMENS IN SOUTHERN AUSTRIA

A 30-year retrospective survey

submitted by

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under supervision of

Univ. Doz. Dr. Cord Langner

Dr. Marion Pollheimer

Graz, 14.05.2019

Affidavit

I hereby declare that the following thesis has been written by myself and without any assistance from third parties. For preparation of this thesis no other sources than those indicated in the thesis itself have been used.

Graz, am 14.05.2019 Carina Hebesberger eh

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Abbreviations

MUG	Medical University of Graz
KAGES	Steiermärkische Krankenanstaltengesellschaft m.b.H. (Styrian hospital society)

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Abstract

Aims: Acute appendicitis is the most frequent surgical emergency in the western world with a life-time risk of 7-9% for both genders. However, according to Literature data, the life-time risk to undergo appendectomy is 23% for females and 12% for males. We aimed to analyse gender distribution, patient age and date of surgery in the reports of appendectomy specimens diagnosed at the Institute of Pathology (Medical University of Graz).

Methods: During the study period from 1987 to 2016, a total of 56,612 appendectomy specimens were analysed. Data regarding gender, age and date of surgery were available for all cases. Associations between gender, age and date of surgery (classified into categories comprising ten-year intervals) were analysed using the Fisher's exact test or Chi square test, as appropriate. In addition, nationwide appendectomy data provided online by Statistics Austria regarding gender and date of surgery for the time period from 1997 to 2016 were analysed. Associations between gender and date of surgery were analysed using the Chi square test. A total of 1,100 pathology reports were chosen randomly to analyse gender differences regarding the extent of (acute and chronic) inflammation diagnosed on the appendectomy specimens.

Results: Overall, there were 31,625 females (55.9%) and 24,987 males (44.1%), with a female/male ratio of 1.27:1. The female/male ratio showed a significant ($p<0.001$) decrease over time: from 1.31:1 (1987-1996 and 1997-2006) to 1.1:1 (2007-2016). Female predominance was most evident at the age group of 16-25 years. In the age group of 16-25 years, the female/male ratio showed a significant ($p<0.001$) decrease from the first (female/male ratio = 1.85:1) to the third decade (female/male ratio = 1.35:1). The female/male ratio of nationwide appendectomies showed a significant ($p<0.001$) decrease during the provided time period. Appendectomy specimens of women were diagnosed with no/low-grade and high-grade inflammation in 58.4% and 41.6% of cases, in contrast to appendectomy specimens of men that demonstrated no/low grade and high-grade inflammation in 26% and 74% of cases, respectively ($p<0.001$). The percentage of no/low-grade inflammation in female and male appendices decreased over time ($p=0.38$).

Conclusion: Our results support available Literature evidence in that females bear a higher risk to undergo appendectomy than males and more often with no/low-grade inflammation. However, these differences adjusted during the study period, in particular within the last decade. Most probably, a more thorough diagnostic work-up with the use of improved imaging technologies contributed to this adjustment.

Zusammenfassung

Hintergrund: Die akute Appendizitis stellt einen der häufigsten chirurgischen Notfälle mit einem Lebenszeitrisiko von 7-9% für beide Geschlechter dar. Allerdings unterscheidet sich das Lebenszeitrisiko appendektomiert zu werden für Frauen und Männer erheblich (23% bzw. 12%). In unserer Studie haben wir den Zusammenhang zwischen der Geschlechterverteilung, dem Patientenalter und dem Zeitpunkt der Appendektomie der am Institut für Pathologie der Medizinischen Universität Graz diagnostizierten Appendektomiepräparate analysiert.

Methoden: Es wurden 56,612 Appendektomiepräparate im Zeitraum von 1987 bis 2016 analysiert. Das Datengut beinhaltete Daten bezüglich Alter, Geschlecht und Zeitpunkt der Appendektomie. Die statistische Auswertung der Daten erfolgte mittels Chi-Quadrat-Test bzw. Fisher-Test. Zusätzlich wurden nationale Appendektomie-Daten bezüglich Geschlecht und Zeitpunkt der Appendektomie im Zeitraum von 1997 bis 2016, online bereitgestellt von Statistik Austria, mittles Chi-Quadrat-Test ausgewertet. Weiters wurden 1100 zufällig ausgewählte histopathologische Diagnosen hinsichtlich des Ausmaßes an (akuter und chronischer) Entzündung und Unterschiede ebenjener zwischen Frauen und Männern analysiert.

Ergebnisse: Insgesamt wurden 31,625 Frauen (56%) und 24,987 Männer (44%) mit einem Geschlechterverhältnis von 1.27:1 in die Studie eingeschlossen. Das Geschlechterverhältnis hat sich im Laufe der Studienzeit signifikant ($p<0.001$) verringert. Der größte Unterschied im Geschlechterverhältnis (weiblich zu männlich) konnte in der Altersgruppe der 16-25-Jährigen festgestellt werden, welches sich signifikant ($p<0.001$) verringerte (von 1.85:1 [1987-1996] zu 1.1:1 [2007-2016]). Das Geschlechterverhältnis der nationalen Appendektomie-Daten hat sich im Laufe des untersuchten Zeitraumes ebenfalls signifikant ($p<0.001$) verringert. Die Appendixpräparate von Frauen bzw. Männern wurden in 58.4% bzw. 26% der Fälle mit keiner oder leichtgradiger Entzündung und in 41.6% bzw. 74% der Fälle mit hochgradiger Entzündung diagnostiziert ($p<0.001$). Die mit keiner oder leichtgradiger Entzündung diagnostizierten Fälle verringerten sich im Laufe des untersuchten Zeitraums ($p=0.38$).

Schlussfolgerung: Unsere Daten sind vergleichbar mit anderen Daten in der Literatur, die zeigen, dass Frauen verglichen mit Männern einem höheren Risiko unterliegen, appendektomiert zu werden. Das Geschlechterverhältnis hat sich während der Studiendauer verringert, vor allem in der letzten Dekade. Bessere diagnostische Möglichkeiten, vor allem die verbesserte bildgebende Diagnostik, sind sehr wahrscheinlich verantwortlich für diese Ergebnisse.

Introduction

Epidemiology

Acute appendicitis is one of the most common acute conditions of the abdomen requiring emergency surgery. Incidence rates of acute appendicitis are highly variable throughout the world with overall incidence rates of about 100 cases per 100,000 population in Europe and the United States (1-4) and lower incidence rates of, e.g., 15 cases per 100,000 population in South Africa. (5) In Asian countries, however, higher incidence rates of, e.g., 227 cases per 100,000 population in South Korea, are seen. (6) In general, in the western world, incidence rates are decreasing since the second half of the 20th century and have stabilized at the end of the 20th century, (1, 4, 7-11) whereas in newly industrialized countries in Southern America, Asia, the Middle East and Africa, incidence rates are increasing since the beginning of the 21st century. (1, 12)

The incidence of acute appendicitis is highly age-dependent, showing a peak at the age of 10-19 years and 15-24 years. (13, 9) Among children, the age-specific incidence is highest at the age of 10-14 years. (4) Appendicitis rates are higher in male than in female patients (4-7, 9, 10) and male patients bear a higher lifetime-risk than female patients to suffer from acute appendicitis. (14) Data from California show a higher incidence of acute appendicitis in the White and Hispanic population than in African Americans and Asians (15). In addition, in many studies a seasonal peak in the summer months is described. (6, 7, 15, 16)

One severe complication of acute appendicitis is organ perforation. Perforation rates strongly vary in different studies ranging between 10% and 30%. (3, 11, 17) The risk for organ perforation is increasing with advanced age from 20% in younger patients to above 50% in patients 80 years or older. (3) According to Literature data, mortality rate is low with rates of about 0.3%. (16, 17)

Appendectomies are numbered among the most common surgical interventions with incidence rates of about 100 to 150 cases per 100,000 population in Europa and about 100 cases per 100,000 population in the United States, which were steadily decreasing in the past decades. Appendectomy rates are higher in Asia (about 200 cases per 100,000 population) and lower in Africa (about 15 cases per 100,000 population), reflecting the incidence rates of acute appendicitis in these countries. (1) The life-time risk of a child aged less than 5 years to undergo appendectomy is higher for females (23.1%) than for males (12.0%). (14)

Pathogenesis

To date, various pathogenetic factors are known to be associated with an increased risk for the development of appendicitis. However, still many of the influencing factors remain unknown. Known influencing factors include luminal obstruction, infection, positive family history, hygienic and dietary factors, ischemia, trauma, environmental factors, and foreign bodies as well as type I hypersensitivity reaction. (18, 19)

Luminal obstruction caused by scars, coprolites, tumours, polyps, metastases, oedemas, foreign bodies and lymphoid hyperplasia might be a causative factor for the development of appendicitis. However, the role of obstruction in acute appendicitis is still not entirely clear. If the lumen is obstructed completely, appendicitis is likely to follow. In contrast, luminal obstruction has been found more often in non-inflamed than in inflamed appendices, especially lymphoid hyperplasia and coprolites. Lymphoid hyperplasia is more common under non-inflamed conditions. Often, there cannot be found a cause of obstruction in appendicitis specimens. Some authors speculate that obstruction might be rather the result and not the cause of the inflammatory process in the appendix. (18-20)

Pathogens involved in acute appendicitis are bacterial agents like E. coli, streptococcus, campylobacter, actinomycosis and yersinia. Viruses such as cytomegalovirus, measles, adenovirus and Epstein-Barr virus have also been shown to play a role as pathogens. There has been evidence that viral infection causes mucosal ulcers, followed by secondary bacterial infection. (21)

In appendectomy specimens, endoparasites like oxyures, schistosoma and strongyloides as well as amebiasis might be found in the lumen. However, schistosomes, strongyloides and amebas are rarely associated with appendicitis and the role of oxyures in appendicitis is controversial. They might be involved by causing luminal obstruction and mucosal ulceration further leading to inflammation. (21)

Positive family history has been shown to play a role in the pathogenesis of acute appendicitis increasing the relative risk up to three times compared to patients with negative family history. According to Literature data, parents of patients with appendicitis were 10% more likely to have a positive medical history than parents of the control group. Exogenous and endogenous factors within a family, including dietary factors (e.g. low fibre intake), bacterial infections, as well as genetic differences in the resistance to bacterial infections, might explain the increased familial occurrence of acute appendicitis. (22)

Pathological features

Macroscopy

In early stage of phlegmonous appendicitis, initial macroscopical changes include presence of a dull serosa which is usually smooth and glistening, together with dilated serosal and subserosal vessels. As the disease progresses, the appendix increases in diameter due to oedematous swelling of the wall. Intramural abscesses can occur. In the setting of gangrenous acute appendicitis, the appendix shows a purple, green or black coloration. (Figure 1) Periappendicitis can occur either with a normal or dull serosa with varying signs of congestation. Fibrinopurulent serosal exsudate is often seen. (18)

Figure 1: Acute appendicitis: the organ is oedematous, the serosal surface appears black to reddish and shows diffuse yellow coating.

Histology

The histopathological findings in acute appendicitis are heterogeneous ranging from minor histopathological signs of inflammation to severe inflammatory or even phlegmonous patterns. In cases with minor histopathological changes, three histological patterns with normal macroscopic appearance have been described. Among these histological changes, active intraluminal inflammation with neutrophils only in the lumen lacking transmural infiltration or mucosal ulceration is described. Since this pattern is not likely to have any influence on the patient's symptoms and has been found in incidentally removed appendices, it should not be diagnosed as true appendicitis. The second pattern is the acute mucosal inflammation or catarrhal inflammation, where neutrophils can be found in the mucosa and occasionally in the lumen sometimes with concomitant mucosal ulceration. The third pattern is the active mucosal and submucosal inflammation with neutrophils in the mucosa and submucosa and additional mucosal ulceration. Pathogenetically, nonspecific infections of the bowl are most likely to be the causative event in these cases. (18)

Phlegmonous or suppurative appendicitis is characterized by a transmural neutrophilic infiltration of the mucosa, submucosa and muscularis propria. Additional pathological changes include mucosal ulceration, oedema of the appendix wall, intramural abscesses and vascular thrombosis. This pattern typically leads to the cardinal symptom of right iliac fossa pain. (18) (Figure 2, Figure 3, Figure 4, Figure 5)

Gangrenous acute appendicitis is characterized by a necrosis of the wall and extensive mucosal ulceration. In untreated cases perforation is likely to follow. (18) (Figure 6)

Periappendicitis is defined as serosal inflammation of the appendix and the surrounding adipose tissue without mucosal involvement. It is characterized by an inflammatory infiltrate in the serosa and subserosa which possibly spreads to the muscularis propria. The lumen stays unaffected. It has to be mentioned that mild diffuse neutrophilic infiltrates in the serosa and in the subserosal vessels may be the result of pre- and intraoperative mechanical manipulation of the appendix. (18, 23) (Figure 7)

Periappendicitis is classified in juvenile and secondary type. Juvenile type is the consequence of earlier episodes of appendicitis showing no evident mucosal inflammation anymore. (23) Secondary periappendicitis is caused by different extra-appendiceal primary and secondary inflammatory conditions, such as pelvic inflammatory disease, chronic inflammatory bowel disease, carcinoma of the gastrointestinal tract, ovarian neoplasia, pseudodiverticulitis or urologic disease. (18, 23)

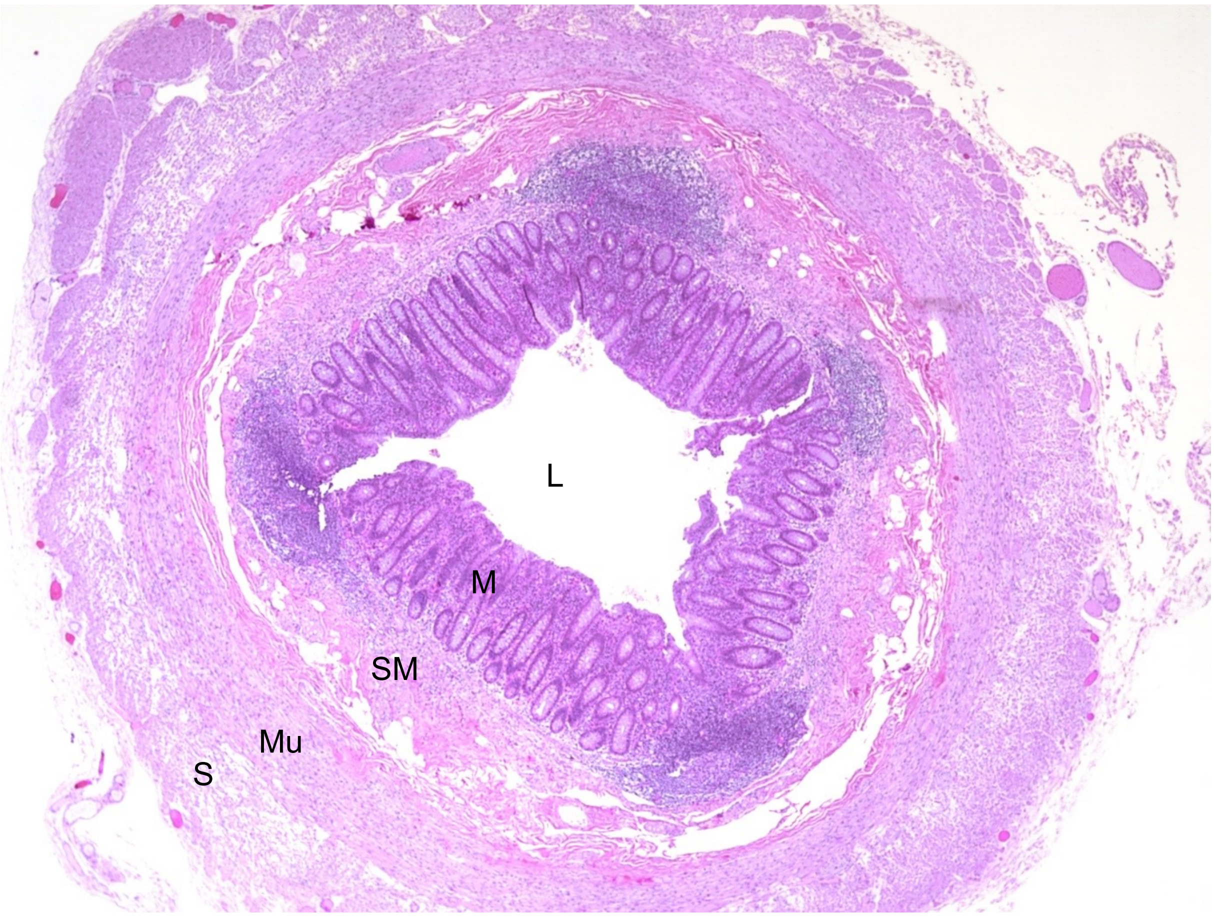

Figure 2: Histoanatomy of the appendix with tunica mucosa (includes lamina epithelialis, lamina propria, and lamina muscularis mucosae), tunica submucosa, tunica muscularis (includes stratum circulare and stratum longitudinale) and tunica serosa. There are lymph follicles in the lamina propria and tunica submucosa. L, lumen; M, mucosa; SM, submucosa; Mu, tunica muscularis propria; S, serosa.

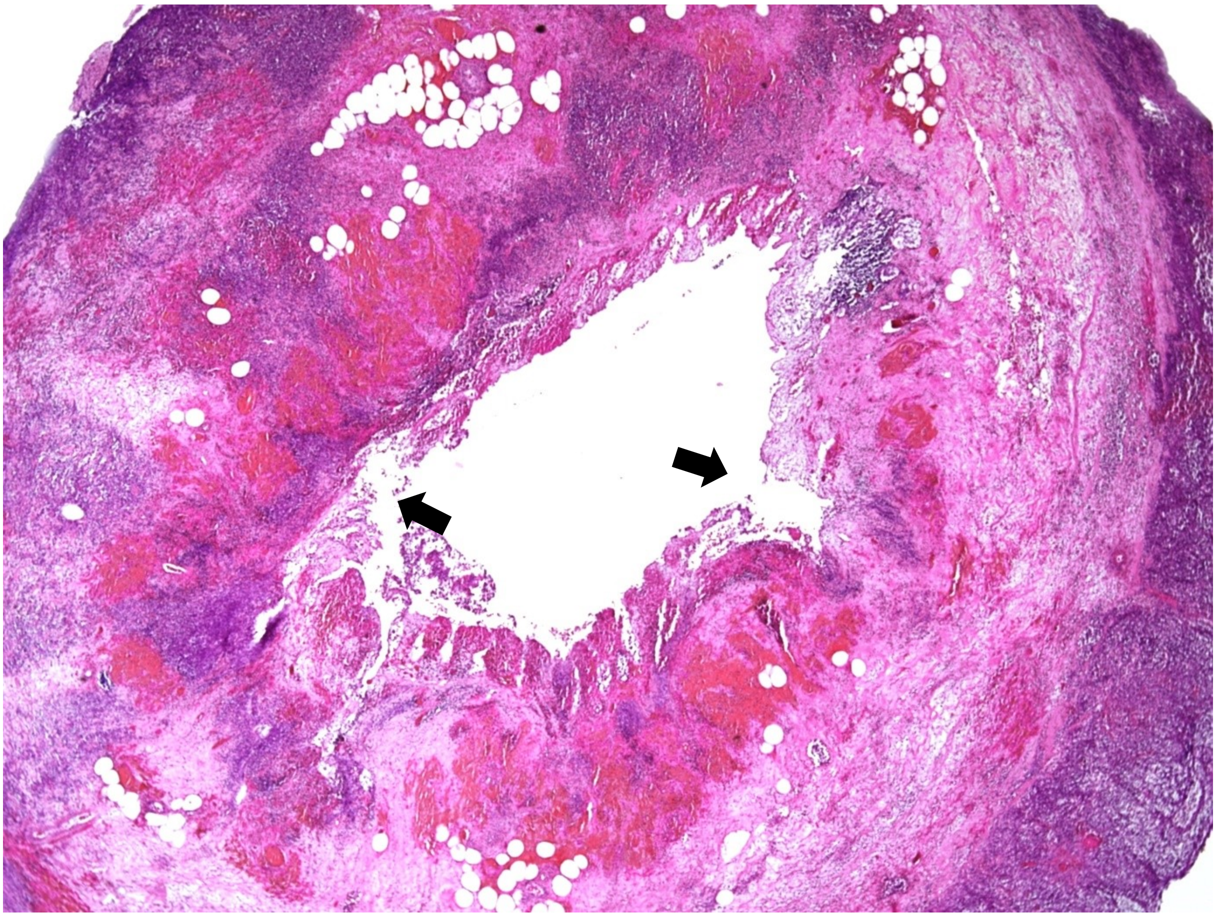

Figure 3: Phlegmonous appendicitis with mucosal ulcerations (arrows), haemorrhage and transmural neutrophilic infiltration of the tunica mucosa, tunica submucosa and tunica muscularis.

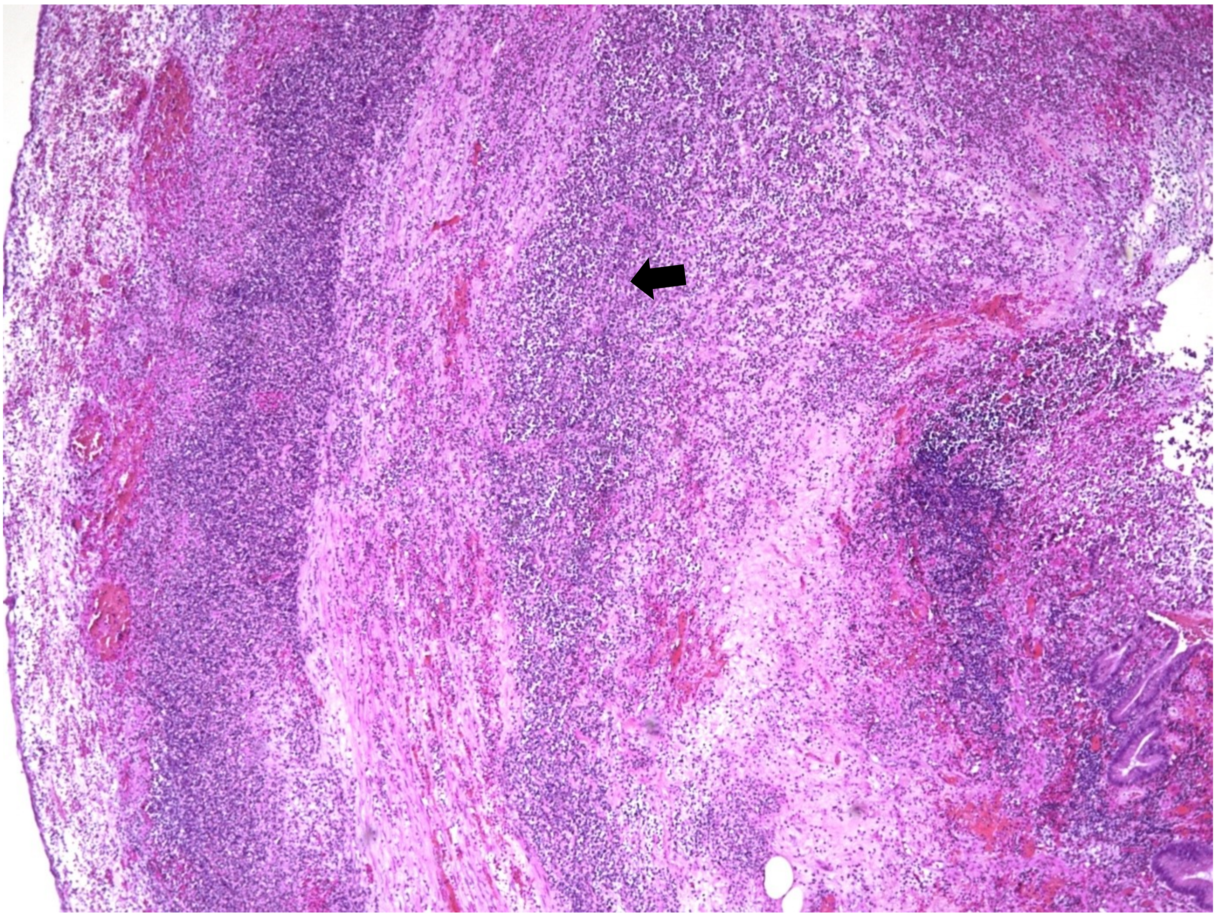

Figure 4: Phlegmonous appendicitis with a transmural abscess (arrow) and ulcerations.

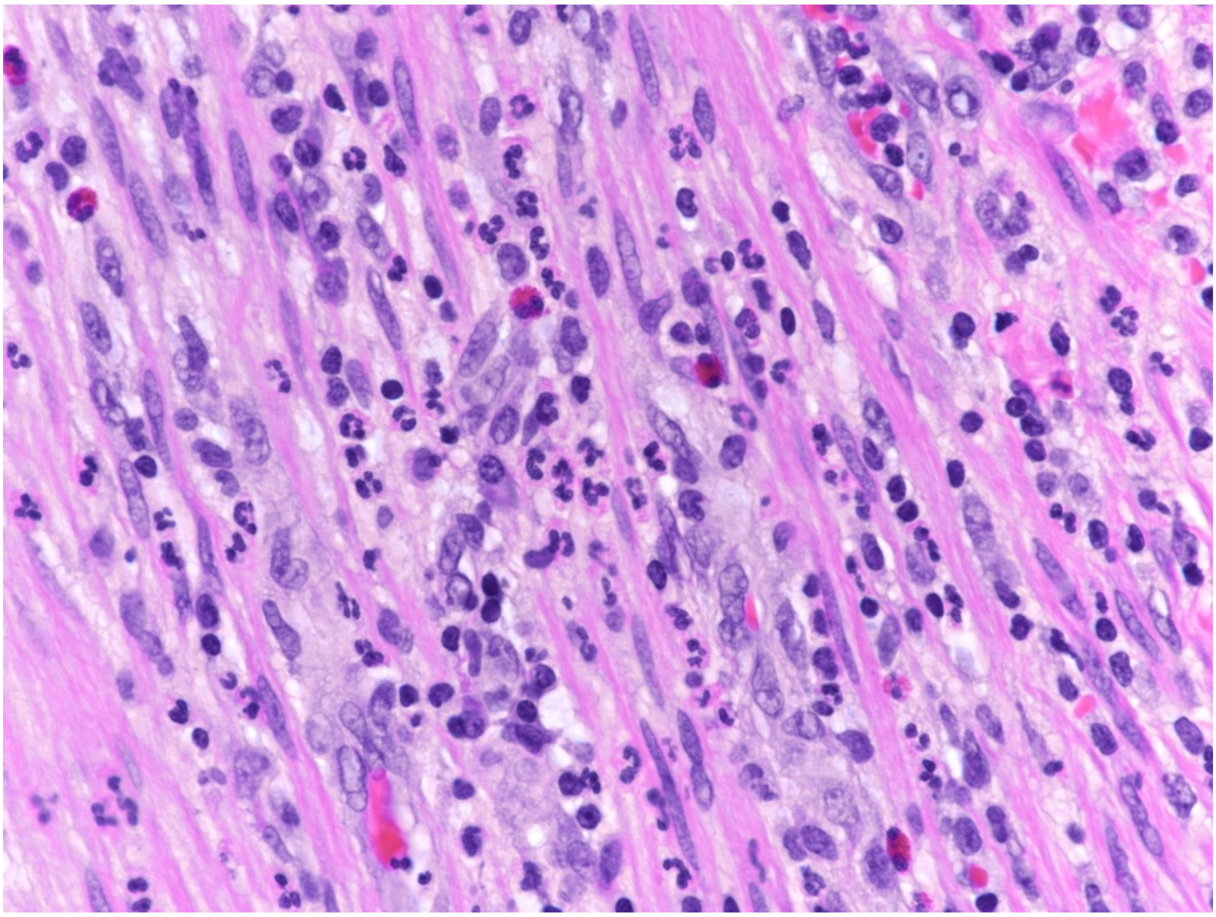

Figure 5: Phlegmonous infiltration with mainly neutrophils in the lamina muscularis propria.

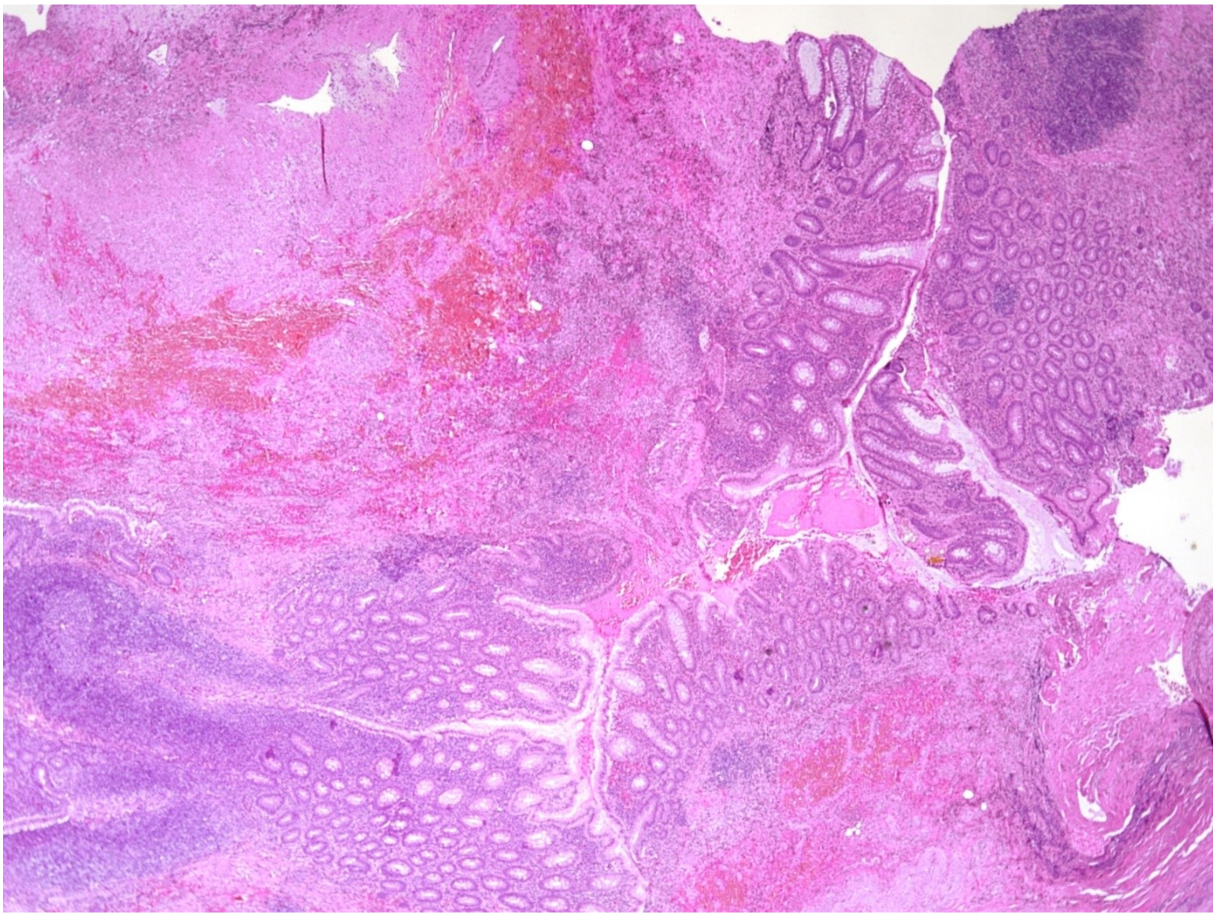

Figure 6: Perforation of the appendix in gangrenous appendicitis.

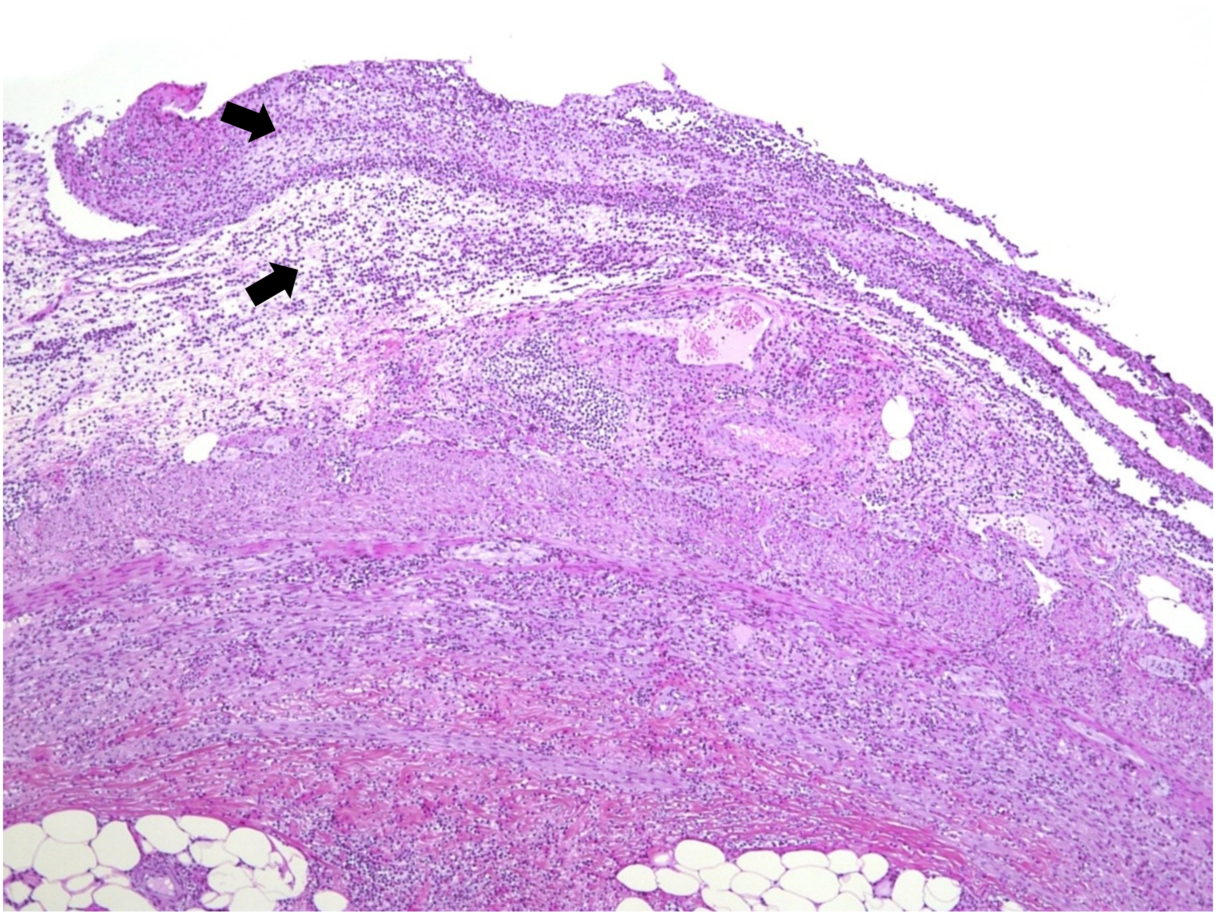

Figure 7: Fibrinous purulent periappendicitis showing extensive neutrophilic infiltration of the subserosa and serosa (arrows) in phlegmonous appendicitis.

Unusual findings of the appendix

Granulomatous appendicitis

Granulomatous appendicitis is an uncommon entity in appendectomy specimens. Histologically, Crohn-like histological features, including granulomas, mural fibrosis, transmural chronic inflammation with lymphoid aggregates and mucosal distorsion are visible. However, only few of the patients will develop systemic Crohn’s disease. The cases present with acute appendicitis and perforation and are primarily treated with antibiotics and followed by delayed appendectomy. This leads to the conclusion that the granulomatous pattern is a sign of subacute/chronic appendicitis due to delayed appendectomy. (24)

Chronic (recurrent) appendicitis

The clinicopathological existence of chronic appendicitis is controversial and there is consensus that the diagnosis ‘primary chronic appendicitis’ should not be made clinically and histologically. (25) There are patients suffering from recurrent episodes of acute appendicitis finally resulting in appendectomy. Affected patients may have chronic symptoms due to coprolithes, adhesions, peri-appendiceal abscesses or specific infections of the appendix. (26) Sometimes the diagnosis is made generously upon appendectomy specimens without evident pathological findings. (27)

Nevertheless, chronic (recurrent) appendicitis is clinically defined by appendicitis symptoms that have lasted weeks to months. Histologically, infiltration of lymphocytes, histiocytes, eosinophils and plasma cells with fibrosis in the lamina propria with or without hyperplasia of the lymphatic tissue is seen. (27) The presence of fibrosis without inflammation and few lymphocytes outside of lymphoid follicles should not lead to the diagnosis of chronic appendicitis. (25)

Neurogenic appendicopathy

Neurogenic appendicopathy is defined as neuroma-like proliferation of nerval structures of the appendix wall. (27) It is clinically indistinguishable from acute or recurrent appendicitis due to similar symptoms such as abdominal pain in the right lower quadrant. (28)

It cannot be differentiated from an unsuspicious appendix macroscopically while surgery. Histologically, three types of neurogenic appendicopathy can be distinguished. In the mucosal type, nerval proliferation is limited to the mucosa. It is characterized by mucosal proliferation which begins at the transition of the lamina muscularis mucosae and leads to dissociation and elevation of the crypts. The mucosal lesion is characterized by S-100-positive Schwann cells replacing the normal lymphocytic cell proliferation in the lamina propria. (Figure 8) Submucous type is characterized by muscular and nerval hyperplastic complexes in the submucosa and an unaltered lamina propria. Axial neuroma type describes an appendix with luminal obliteration by central or axial neuroma with fibrous scar tissue surrounding. (29)

Primary or secondary appendiceal malignancies

Appendiceal tumours have been reported in less than 3% of all appendectomy specimens. The most frequently diagnosed primary malignancy is the carcinoid tumour with an incidence of 0.37% which represents 60% of all appendiceal tumours. (30) Classical carcinoid tumours with less than two centimetre in diameter have low metastatic potential and are usually treated with local resection, whereas larger lesions require right hemicolectomy. (31)

Goblet cell carcinoid is a rare variant of appendiceal carcinoid. Its histopathological features lie between classical appendiceal carcinoid and colonic signet ring cell adenocarcinoma. Its metastatic potential is up to 20%, therefore right hemicolectomy is suggested. (31)

Primary appendicular adenocarcinoma is a rare tumour of the appendix with an incidence of 0.25% (30) accounting for 4-6% of primary malignant appendiceal neoplasms. It is characterized either by a colonic (comparable to adenocarcinoma of the colon) or cystic growth pattern (comparable to ovarian cystadenocarcinoma). (31)

Primary lymphomas of the appendix account for 1.3 to 2.6% of all gastrointestinal lymphomas. Non-Hodgkin-Lymphoma of B-cell origin is the most common primary lymphoma of the appendix. (31)

Metastatic invasion to the appendix is very rare with less than 50 reported cases. Breast cancer is the most common entity. (31)

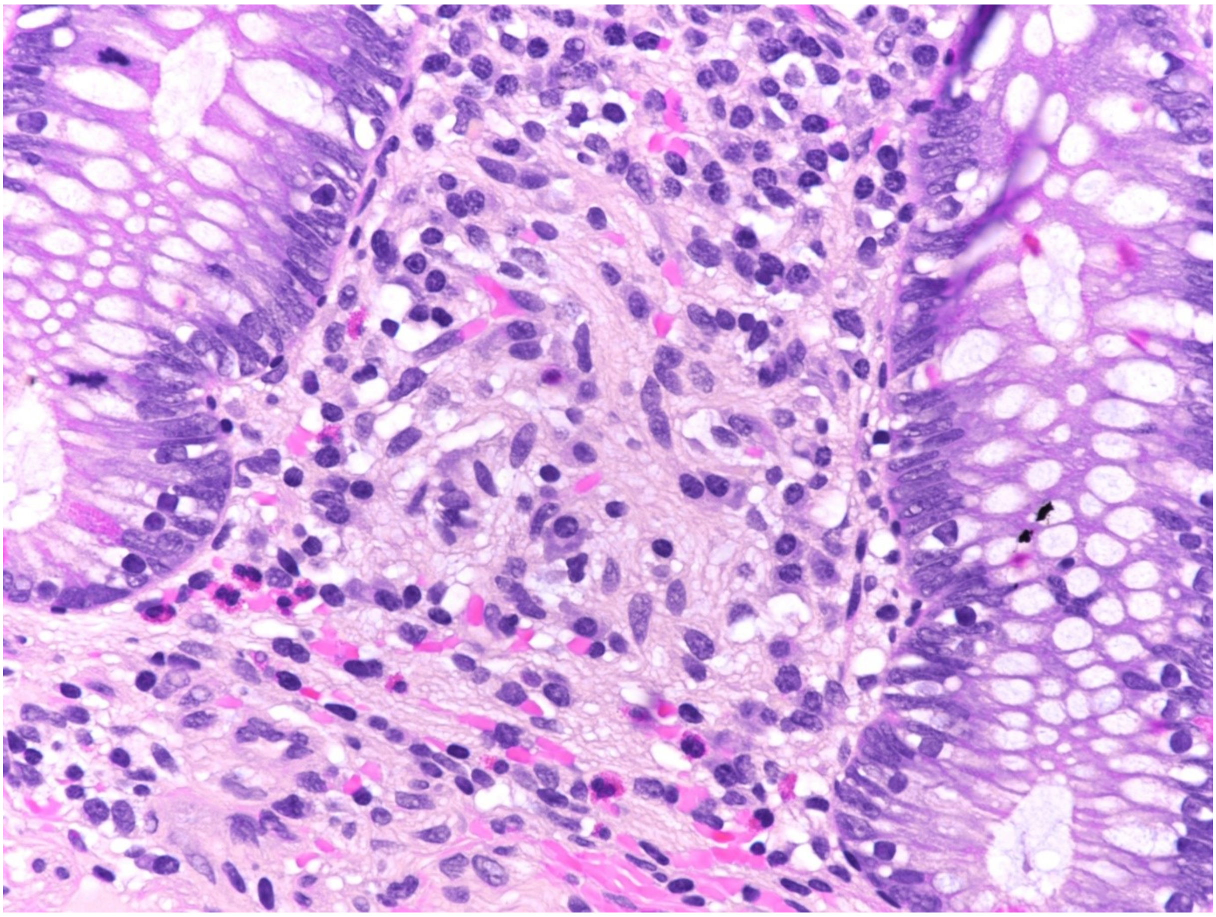

Figure 8: Mucosal type of neurogenic appendicopathy: Neuroma-like proliferation of nerval structures in the mucosa of the appendix.

Clinical symptoms and diagnostic workup

The cardinal clinical symptom of acute appendicitis is abdominal pain of short duration. Initially the pain is located in the epigastric or periumbilical area and migrates to the right lower abdominal quadrant near Mc Burney's point during the disease progress. Other clinical symptoms include anorexia, nausea, vomiting, and a slightly increased body temperature. (32, 33)

Diagnostic workup includes clinical history, physical examination, serological analysis and radiological investigation. Under certain circumstances, diagnostic laparoscopy might be used. (32)

Clinical history and physical examination show a diagnostic accuracy of 68% with a sensitivity of 67% and a specificity of 100%. The most common clinical sign in physical examination is abdominal pain and tenderness centered in the right lower abdominal quadrant which is present in 95% of all cases. Blumberg's rebound pain, pain in the right lower abdominal quadrant during percussion and palpation of the left lower quadrant (Rovsing sign), pain in the right lower abdominal quadrant during extension (psoas sign) and during flexion and internal rotation of the right hip (obturator sign) appear in less than 40% of all patients. Temperature difference higher than 1°C between axillary and rectal temperature is a sign of pelvic inflammation either due to acute appendicitis or other pelvic inflammation. (32, 34)

Serological analysis and interpretation of inflammatory markers play a minor role in diagnostic workup showing a diagnostic accuracy of 37%. Neither C-reactive protein nor white blood cell count and procalcitonin were shown to be sensitive diagnostic tools. Increase of C-reactive protein might be used as an ancillary diagnostic tool and indicator of the inflammatory activity. Procalcitonin has high diagnostic value in differentiating complicated (perforated) from uncomplicated acute appendicitis. (34, 35)

Preoperative imaging supports clinical diagnosis. Transabdominal or transvaginal sonography, computed tomography and magnetic resonance tomography might be used. (32)

Transabdominal sonography is rapid, readily available, cheap, non-invasive and there are no described contra-indications. However, its diagnostic value is limited to obesity, peritoneal reaction with muscular tension of the abdomen, overlay of intestinal gas and particularly due to the operator’s skill. The diagnostic accuracy of sonography is moderate reaching a sensitivity of 77% and a specificity of 37%. (32, 34) In children, transabdominal sonography may be preferred due to the greater need in radiation prevention, less abdominal fat and thinner abdominal muscle wall. (19)

Computed tomography is an excellent alternative diagnostic tool when diagnosis remains unclear after physical examination and sonography. Sensitivity and specificity have been reported to be 98% and 89%. Use of computed tomography increased during the 21st century with several studies showing a decrease of negative appendectomy rate when using computed tomography routinely. (32, 36-38)

Magnetic resonance tomography plays a minor role in the diagnostic workup of acute appendicitis but might be used as an alternative tool instead of computed tomography in pregnant women or patients who suffer from allergy to iodinated contrast material. Diagnostic accuracy is similar to computed tomography with a sensitivity and specificity of 97% and 81%, respectively. (32, 36)

In addition, several clinical scoring systems have been developed to support diagnostic workup and to guide clinical management. Among them, Alvarado Score and RIPASA Score are commonly used. In general, both scoring systems rank the probability for acute appendicitis based on scoring points for symptoms and signs as well as laboratory findings. In the RIPASA scoring system, age and gender is considered as well. Diagnostic accuracy of RIPASA Score is higher than Alvarado score with a sensitivity of 94% and a specificity of 55%, while sensitivity and specificity of Alvarado Score are 69% and 77%, respectively. The scores play a minor part in diagnosing acute appendicitis in the Western world but are helpful diagnostic tools in rural hospitals of developing countries lacking modern imaging technologies. (39)

Therapeutical management

Surgical treatment

Appendectomy is considered the therapeutic gold-standard for uncomplicated and complicated appendicitis with a treatment effectiveness of 99%. It is performed laparoscopically or open. Compared to open appendectomy, laparoscopic surgery reduces the risk of surgical site infections and small bowl obstructions but increases the risk of intra-abdominal abscesses. Further advantages of laparoscopic surgery include less post-operative pain, shorter hospitalisation time and diagnostic value. Patients with complicated appendicitis are treated with post-operative antibiotics to reduce the risk of surgical site infections, bacteraemia and sepsis. The use of antibiotics in all patients prior to surgery is recommended. (40-42)

Conservative treatment

The recent approach of using antibiotics as single treatment for uncomplicated appendicitis is controversial. Intravenous antibiotic therapy covering aerobic and anaerobic bacteria for one to three days under hospital surveillance followed by oral antibiotic therapy for seven to ten days is recommended. Treatment effectiveness has been reported to be as high as 72%. Complication-free treatment success is lower in antibiotic therapy than in surgical therapy. (41)

Aims of the study

We aimed to analyse the reports of appendectomy specimens diagnosed at the Institute of Pathology, Medical University of Graz, within the last thirty years with respect to gender differences in the appendectomy specimens over time and its correlation with the extent of inflammation. In a first step, the development of the female/male ratio was investigated in three different time periods, each accounting for 10 years (1987 to 1996, 1997 to 2006, and 2007 to 2016, respectively). In a second step, the correlation of patient gender with patient age was investigated for the study period and for the three time periods separately. In addition, we analysed 500 (250 of each gender) randomly chosen histopathological diagnoses of the study period and 600 (300 of each gender) randomly chosen histopathological diagnoses of the three different time periods to find out whether the histopathological diagnoses of women and men differed regarding the extent of inflammation.

Materials and Methods

Ethics Board Approval

The retrospective database analysis was approved by the ethics review committee of the Medical University of Graz (EK-number: 30-144 ex 17/18).

Study Cohort

The pathological reports of all appendectomy specimens diagnosed at the Institute of Pathology, Medical University of Graz (MUG) in the period from January 1, 1987 to December 31, 2016 were included in the investigation.

The generated database includes information regarding patient age and gender as well as the date of the surgery. It also provides information regarding the hospital in which the appendectomy was performed. These comprise the University Hospital of Graz (MUG), the hospitals of the KAGES (Styrian hospital society) and other hospitals in Styria (Hospital of Brothers of Mercy Graz, Elisabethinen Graz) and in Carinthia (Hospital of Brothers of Mercy St. Veit an der Glan).

The initial cohort comprised 63,585 patients with 35,389 (55.7%) females and 28,186 (44.3%) males (female/male ratio = 1.26:1).

Patients who did not undergo surgery for presumed appendicitis were excluded from the study. These included the following: (i) patients who underwent appendectomy as part of right hemicolectomy; (ii) patients who underwent appendectomy during visceral resections of other parts of the bowel; and (iii) patients who underwent appendectomy as part of primarily gynaecologic surgery.

In total, 56,612 patients out of 63,585 (89.0%) were included in the final investigation (study cohort). Among these, 31,625 (55.9%) patients were female and 24,987 (44.1%) patients were male (female/male ratio = 1.27:1) (Figure 9). 20,088 (35.5%) patients underwent appendectomy in the University Hospital of Graz, 31 067 (54.9%) in the KAGES-hospitals and 5,457 (9.6%) in the remaining hospitals, respectively. (Figure 10)

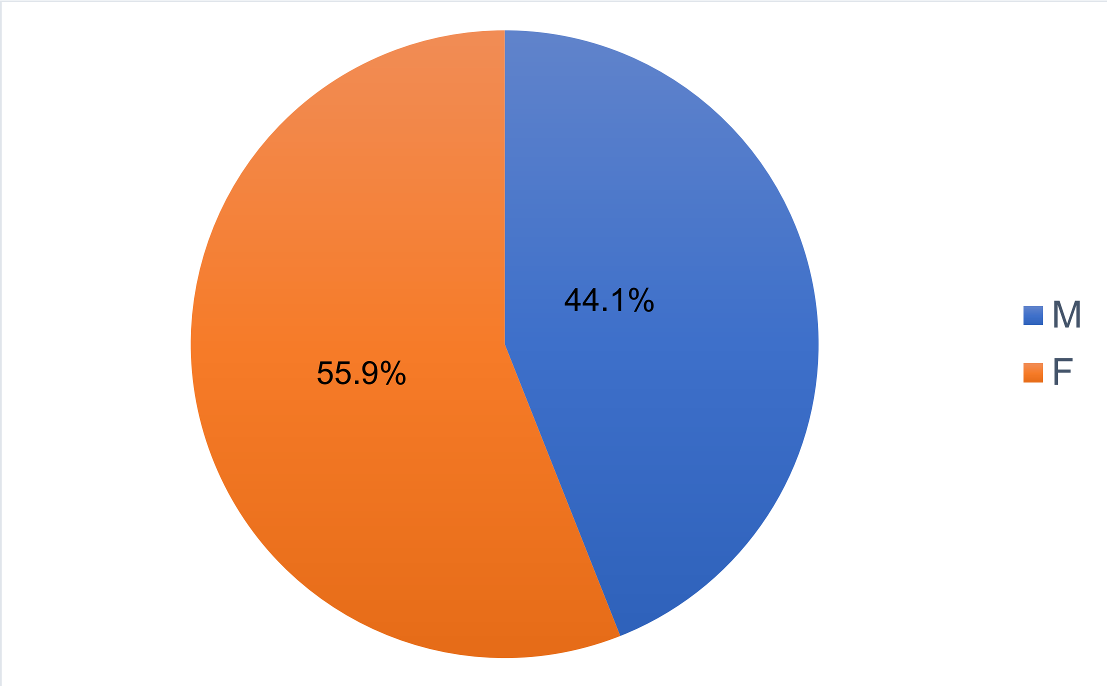

Figure 9: Gender distribution in the study cohort.

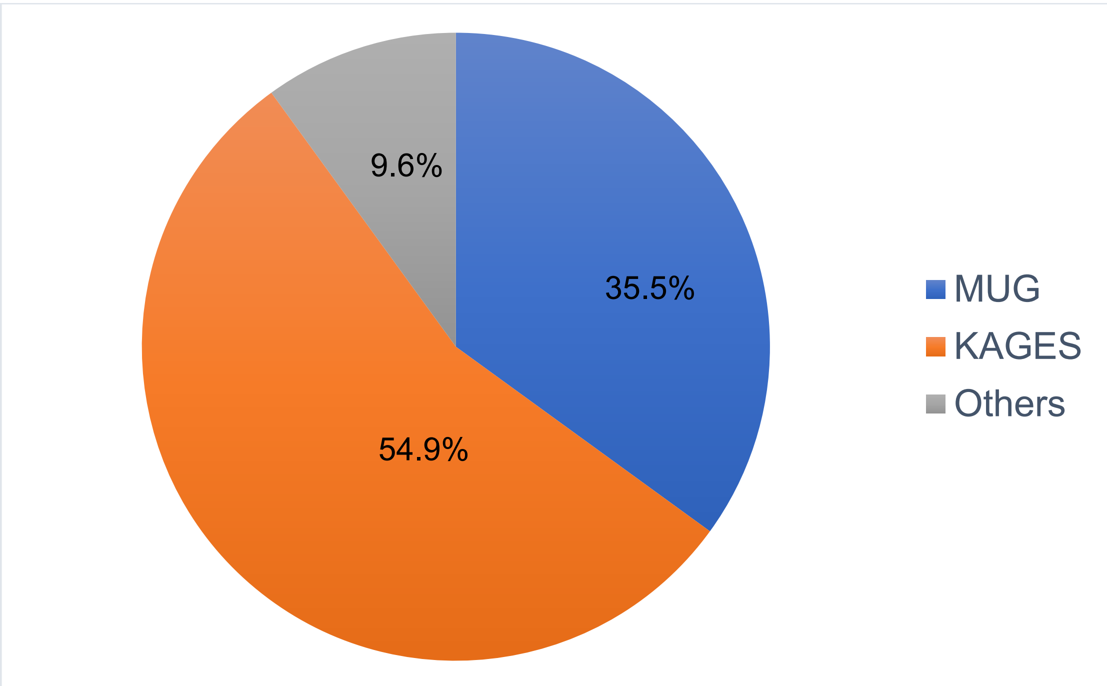

Figure 10: Hospitals where the appendectomies were performed.

Analysis of nationwide appendectomy data (Statistics Austria)

The national database Statistics Austria provides data of appendectomy numbers and gender distribution in the time span from 1997 to 2016. These nationwide data were analysed to compare with the data from the Institute of Pathology within the same time span.

The data set includes a total of 322,599 patients with 172,124 (53.4%) females and 150,475 (46.6%) males (female/male ratio = 1.14:1). (Figure 11)

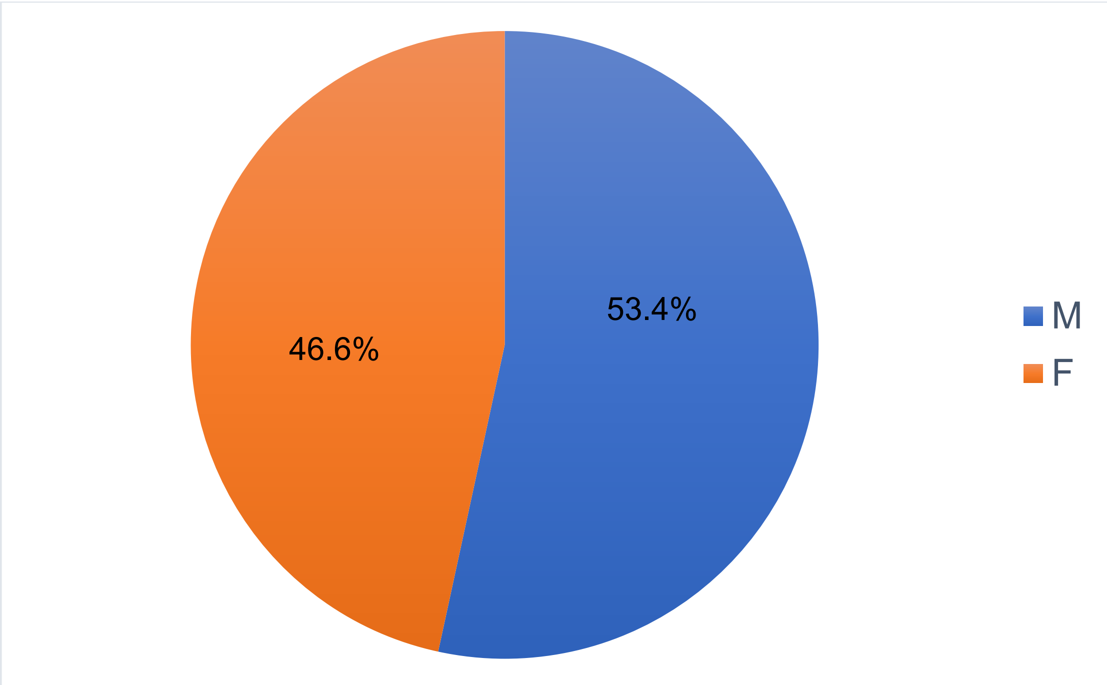

Figure 11: Gender distribution in the nationwide appendectomy data.

Analysis of histopathological reports

Altogether, 1,100 patients (550 females and 550 males) were randomly chosen to analyse the pathology reports regarding the extent of inflammation. The diagnoses were divided into three categories, termed "low-grade inflammation", "high-grade inflammation" and "no acute inflammation", based upon the following criteria:

- Low-grade appendicitis includes the following diagnoses: acute mucosal inflammation, catarrhal appendicitis and mildly active appendicitis.
- High-grade appendicitis includes the following diagnoses: phlegmonous appendicitis, suppurative appendicitis, and gangrenous appendicitis (with or without perforation).
- No acute inflammation includes the following diagnoses: postinflammatory changes such as fibrosis (with or without lumen obliteration), neurogenic appendicopathy, coprolite, oxyuriasis, and normal appendix.

Statistical analysis

The development of the female/male ratio was investigated in three different time spans, each accounting for a period of 10 years (1987 to 1996, 1997 to 2006, and 2007 to 2016).

In addition, the gender distribution was related to patient age in order to identify a possible relationship. The analysis of patient age was performed by categorizing the patients into eight different age groups (<6, 6-15, 16-25, 26-35, 36-45, 46-55, 56-65 and >65 years). This was done for the whole study period, but also for the three decades separately.

All data listed above are included in a retrospective joint database using Microsoft Excel 2010. Categorical variables were presented as numbers and percentages. Differences in categorical variables were examined using the Fisher's exact test or chi-square test, as appropriate.

All statistical operations were performed using Microsoft Excel 2010 and SPSS, Statistics for Windows, version 24.0 (IBM, Chicago, IL, USA). P-values were two-sided, and values below 0.05 were considered significant.

Results

Population characteristics

The ages of the study cohort ranged from 0 to 99 years with a mean age of 24 years and a median age of 17 years for both genders. The largest age group was the group of the 6-15-year-old patients (39.6%). There were 29,251 (51.7%) patients younger than 18 years (16,220 females and 13,031 males) and 27,361 (48.3%) patients 18 years or older (15,405 females and 11,956 males). (Figure 12)

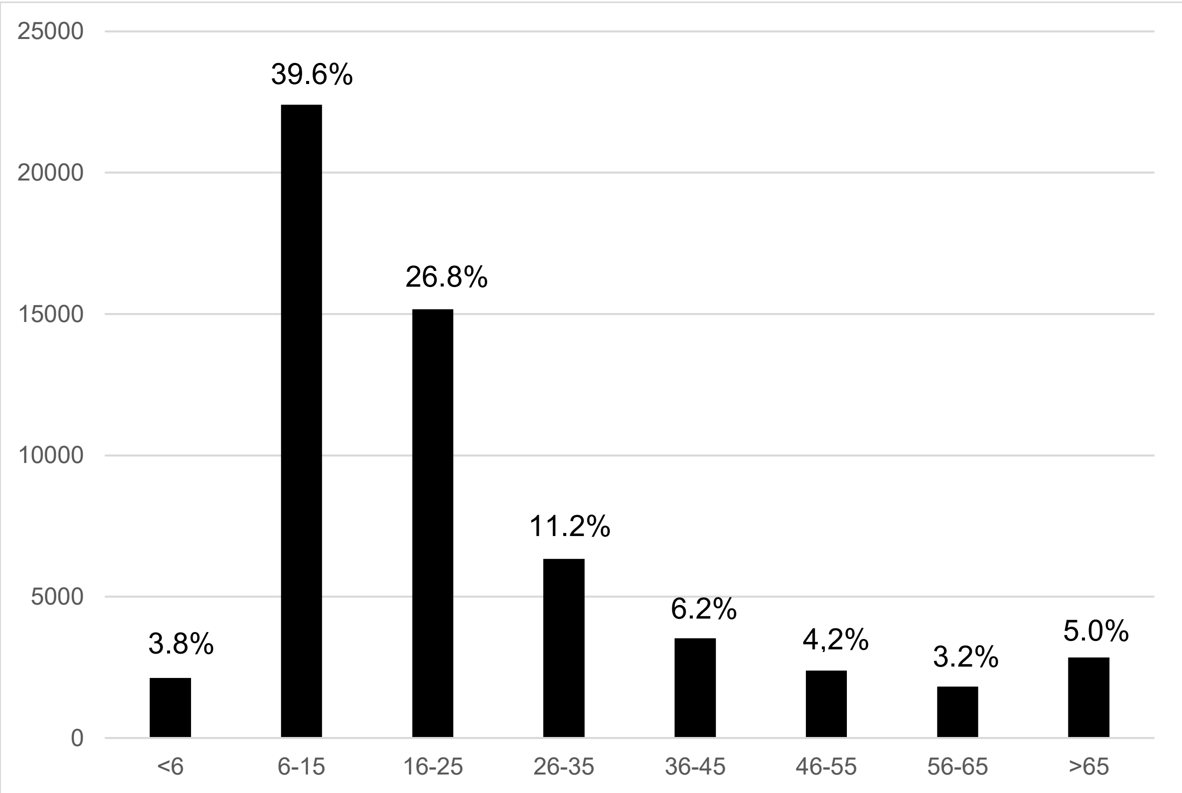

Figure 12: Age distribution in the study cohort.

The cohort of the MUG patients included 10,860 (54.1%) females and 9,228 (45.9%) males. The ages ranged from 0 to 99 years with a mean age of 19 years (19 years for females and 18 years for males) and a median age of 13 years (14 years for females and 12 years for males).

The cohort of the KAGES patients included 17,456 (56.2%) females and 13,611 (43.8%) males. The ages ranged from 0 to 99 years with a mean age of 25 years (24 years for females and 27 years for males) and a median age of 20 years (19 years for females and 20 years for males).

The cohort of the patients of the remaining hospitals included 3,309 (60.6%) females and 2,148 (39.4%) males. The ages ranged from 0 to 92 years with a mean age of 27 years and a median age of 21 years for both genders.

Analysis of gender ratio

Analysis of gender ratio in the study cohort

The female/male ratio decreased significantly ($p<0.001$) from 1.34:1 (1,511 females and 1,128 males) in 1987 to 1.01:1 (373 females and 371 males) in 2016 in the study cohort. (Figure 13, Figure 14)

The greatest difference was observed in 1988, with a female/male ratio of 1.43:1 (1,579 females and 1,106 males). The lowest difference was observed in 2015, with a female/male ratio of 0.95:1.

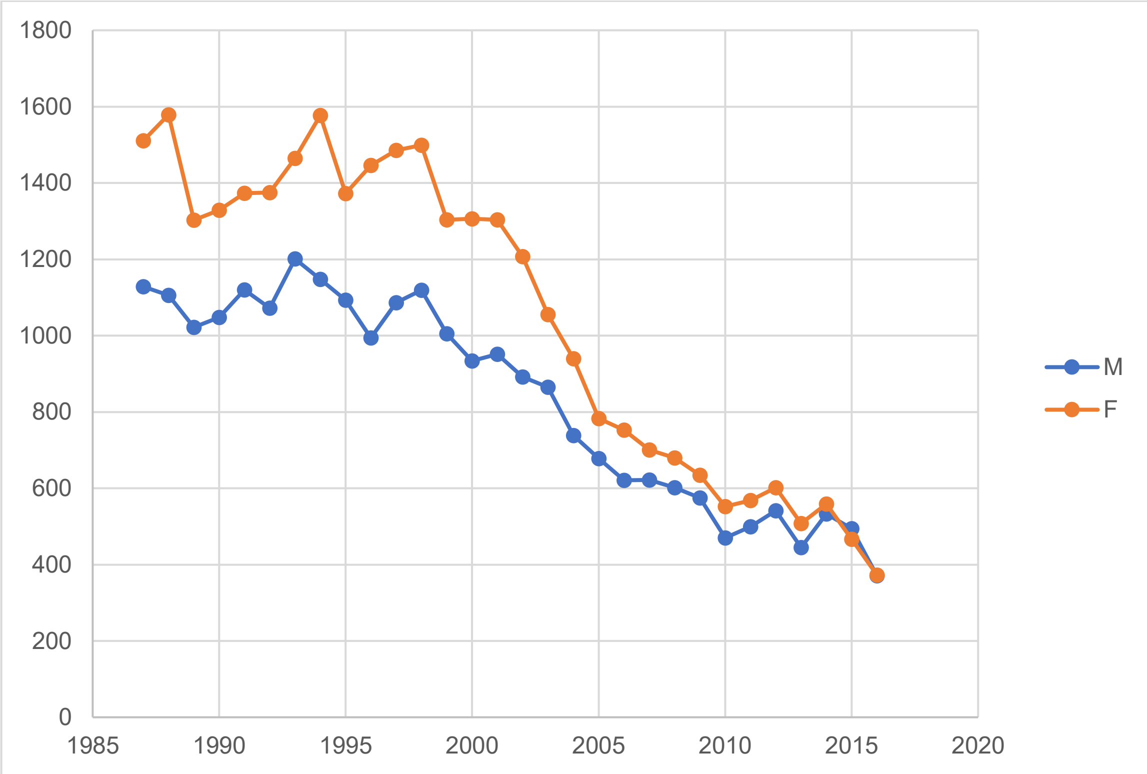

Figure 13: Absolute numbers of appendectomy specimens in the study cohort (shown for females and males separately) during the study period (1987-2016).

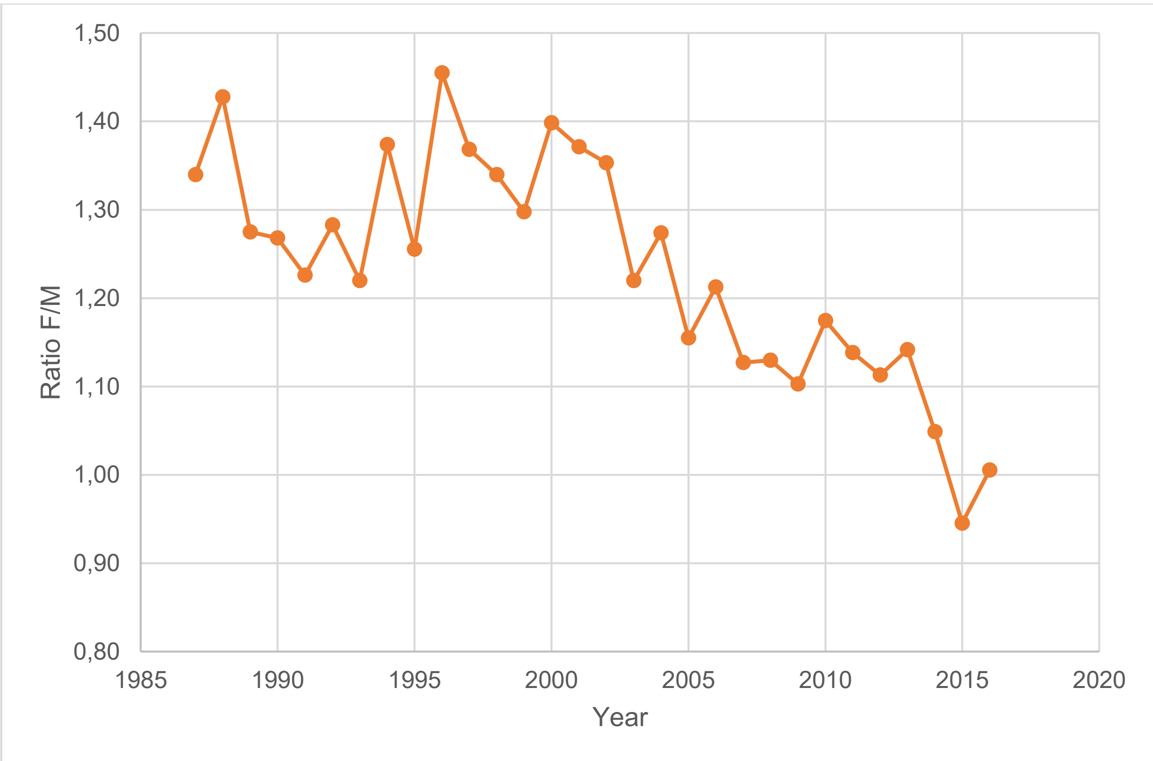

Figure 14: Development of the female/male ratio in the study cohort during the study period.

Analyses of gender ratio regarding the subgroups

The female/male ratio of appendectomy specimens sent from the MUG decreased significantly (p=0.015) from 1996 (female/male ratio = 1.39:1 with 505 females and 363 males) to 2016 (female/male ratio = 1.11:1 with 249 females and 225 males). (Figure 15)

The greatest difference was observed in 1997 with a female/male ratio of 1.42:1 (530 females and 374 males) and the lowest difference was observed in 2005 with a female/male ratio of 0.96:1 (250 females and 261 males), respectively.

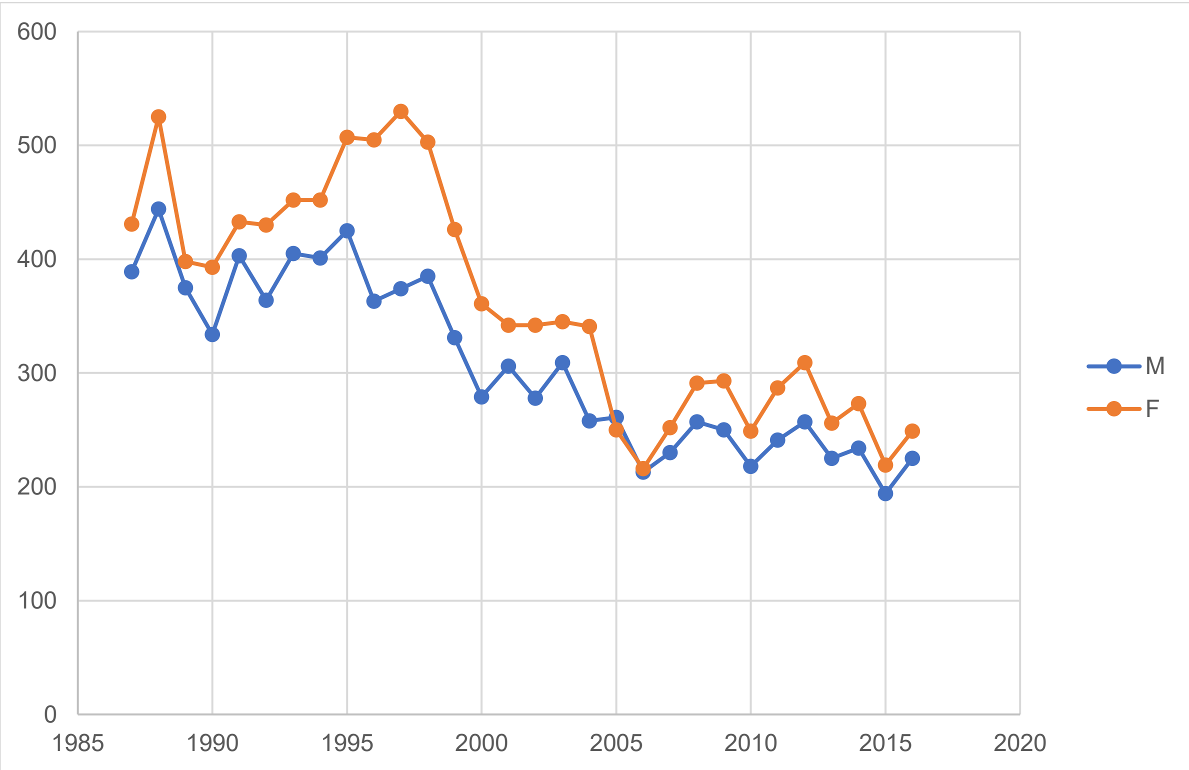

Figure 15: Absolute numbers of appendectomy specimens sent from the MUG (shown for males and females separately) during the study period.

The female/male ratio of the appendectomy specimens sent from the KAGES hospitals decreased significantly (p<0.001) from 1987 (female/male ratio 1.45:1 with 948 females and 653 males) to 2016 (female/male ratio = 0.78:1 with 83 females and 106 males), when the lowest difference was observed. (Figure 16)

The greatest gender difference was observed in 1988 with a female/male ratio of 1.59:1 (928 females and 584 males).

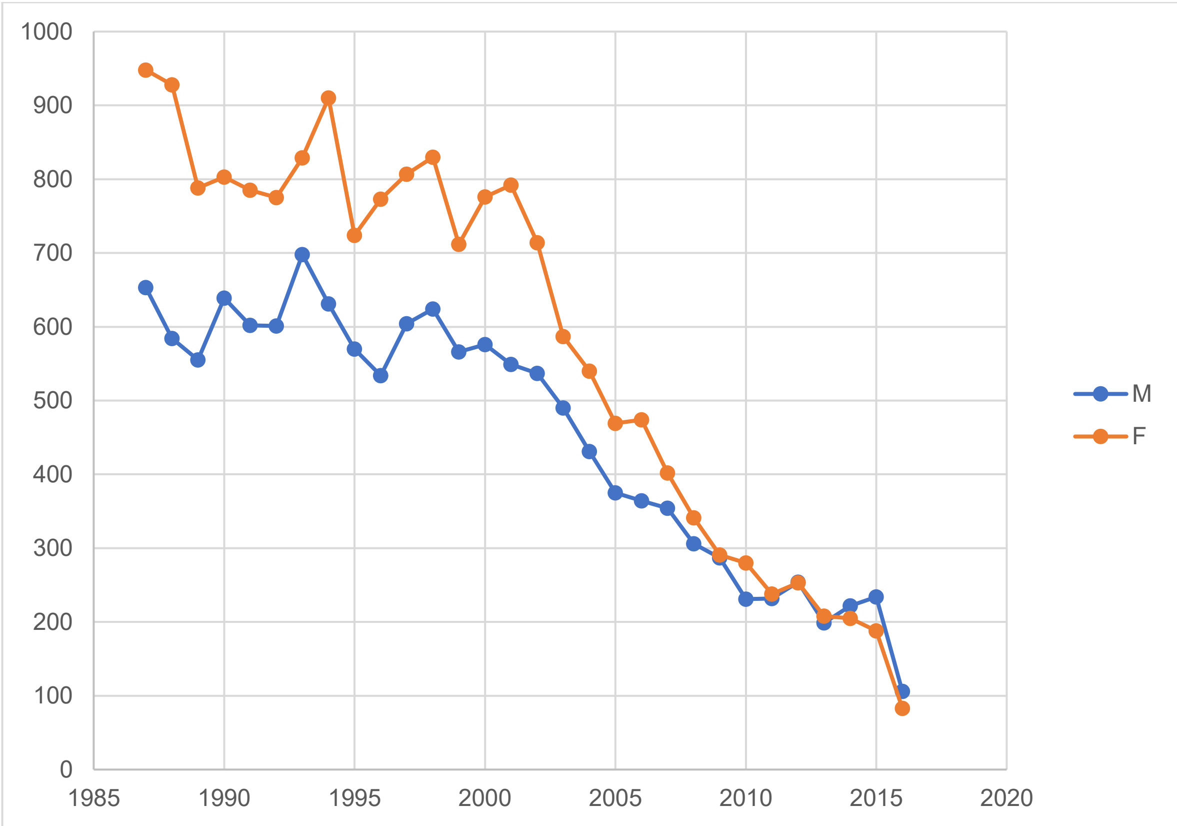

Figure 16: Absolute numbers of appendectomy specimens sent from the KAGES hospitals (shown for males and females separately) during the study period.

The female/male ratio of the appendectomy specimens sent from the remaining hospitals decreased significantly ($p<0.001$) from 1987 (female/male ratio = 1.53:1 with 132 females and 86 males) to 2016 (female/male ratio = 1.03:1 with 41 females and 40 males). (Figure 17)

The greatest gender difference was observed in 2000 (female/male ratio = 2.14:1 with 169 females and 79 males). The lowest gender difference was observed in 2015 (female/male ratio = 1.03:1 with 60 females and 66 males).

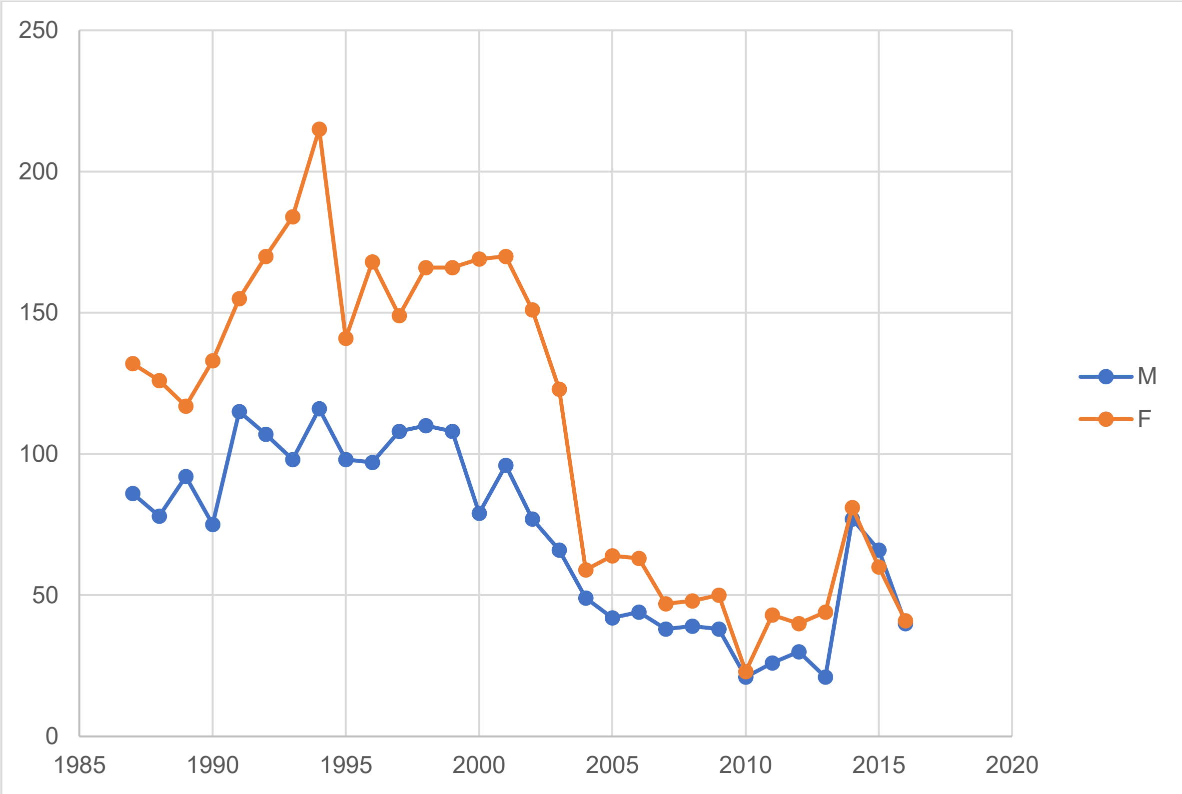

Figure 17: Absolute numbers of appendectomy specimens sent from the remaining hospitals (shown for males and females separately) during the study period.

Analyses of gender ratio regarding the three decades

The female/male ratio showed a significant decrease ($p<0.001$) from the first (1987-1997) and the second (1997-2006) to the third decade (2007-2016). It decreased from a female/male ratio of 1.31:1 in the first and second decade to a female/male ratio of 1.1:1 in the third decade. (Figure 18) This trend was also observed in the analysed subgroups (appendectomy specimens sent from the MUG, the KAGES hospitals and the remaining hospitals). (Detailed data are presented in Table 1, Table 2, Table 3, Table 4).

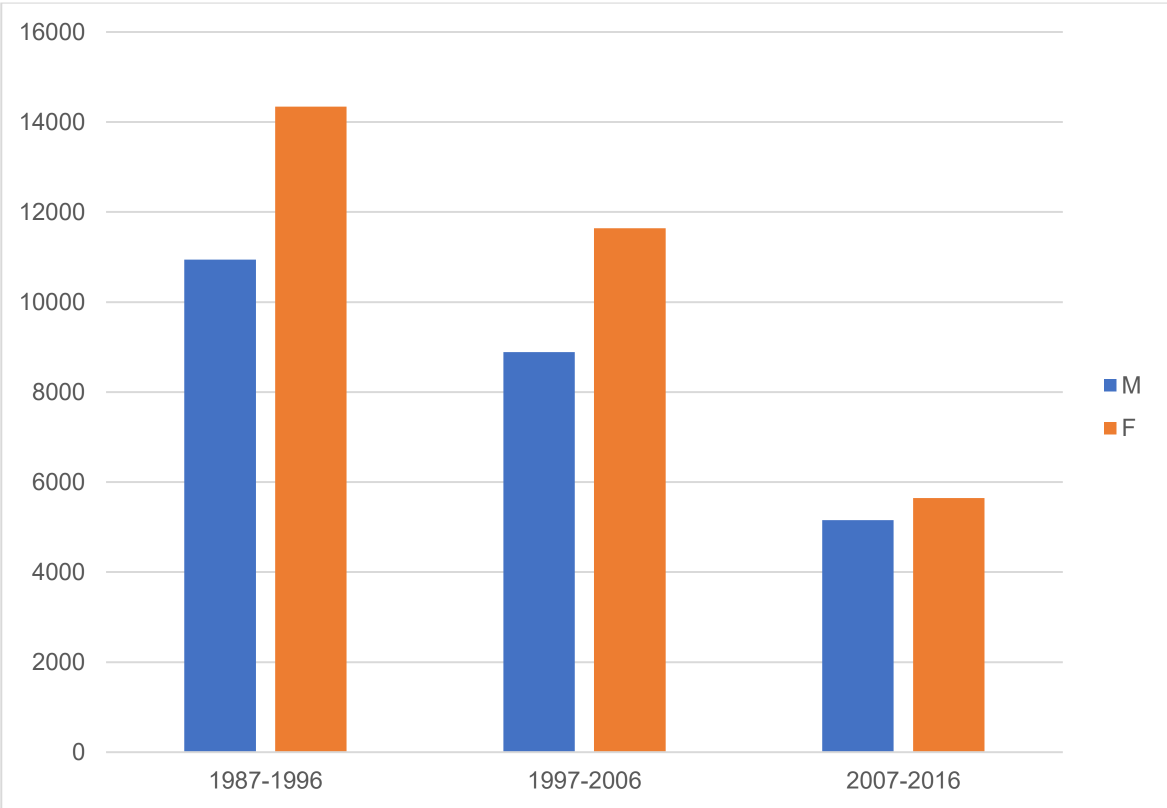

Figure 18: Gender difference of appendectomy specimens in the study cohort shown for all three decades separately.

Table 1: Absolute numbers and female/male ratios of appendectomy specimens in the study cohort separated in three decades.

Study cohort	Females	Males	Ratio F/M
1987-1996	14,343	10,945	1.31:1
1997-2006	11,637	8,890	1.31:1
2007-2016	5,644	5,152	1.10:1

Table 2: Absolute numbers and female/male ratios of appendectomy specimens sent from the MUG separated in three decades.

MUG	Female	Male	Ratio F/M
1987-1996	4,526	3,903	1.16:1
1997-2006	3,656	2,994	1.22:1
2007-2016	2,678	2,331	1.15:1

Table 3: Absolute numbers and female/male ratios of appendectomy specimens sent from the KAGES hospitals separated in three decades.

KAGES	Female	Male	Ratio F/M
1987-1996	8,266	6,070	1.36:1
1997-2006	6,701	5,116	1.31:1
2007-2016	2,489	2,425	1.03:1

Table 4: Absolute numbers and female/male ratios of appendectomy specimens sent from the remaining hospitals separated in three decades.

Others	Female	Male	Ratio F/M
1987-1996	1,551	972	1.60:1
1997-2006	1,280	780	1.64:1
2007-2016	477	396	1.20:1

Analyses of gender differences regarding patient age

Gender difference was significantly ($p<0.001$) most prominent in the age group of 16-25 years (female/male ratio = 1.72:1 with 9,585 females and 5,583 males). (Figure 19)

This trend could also be observed in each subgroup separately (MUG, KAGES and remaining hospitals). When comparing the three subgroups, the most prominent gender difference was observed in the remaining hospitals in the age group of 16-25 years with a remarkable female/male ratio of 2.05:1 (1,111 females and 542 males).

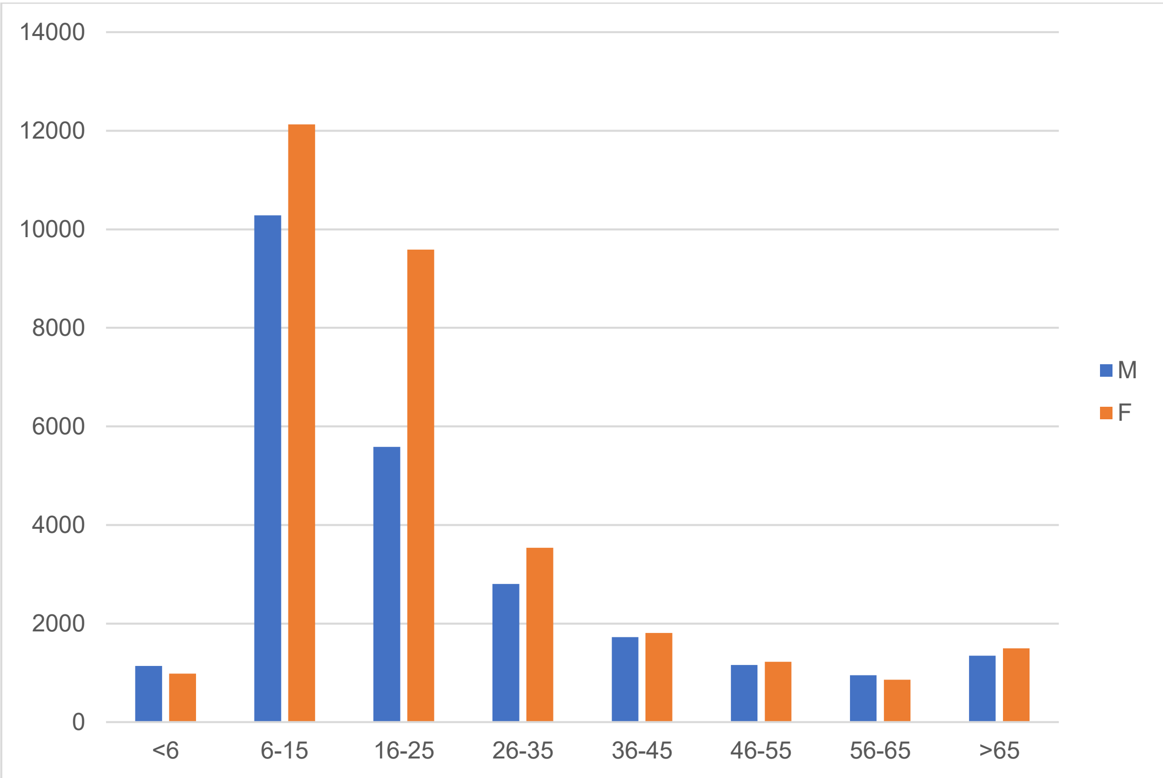

Figure 19: Absolute numbers of appendectomy specimens of females and males related to patient age in the study cohort.

The female/male ratio in the age group of 16-25 years showed a significant ($p<0.001$) decrease during the study period. It decreased from a female/male ratio of 1.85:1 (4,390 females and 2,369 males) in the first decade to a female/male ratio of 1.79:1 (3,431 females and 1,912 males) in the second decade and a female/male ratio of 1.35:1 (1,763 females and 1,302 males) in the third decade. (Data are presented in Figure 20, Figure 21, Figure 22 and Table 5, Table 6, Table 7)

These trends could also be observed in each subgroup separately (MUG, KAGES and remaining hospitals).

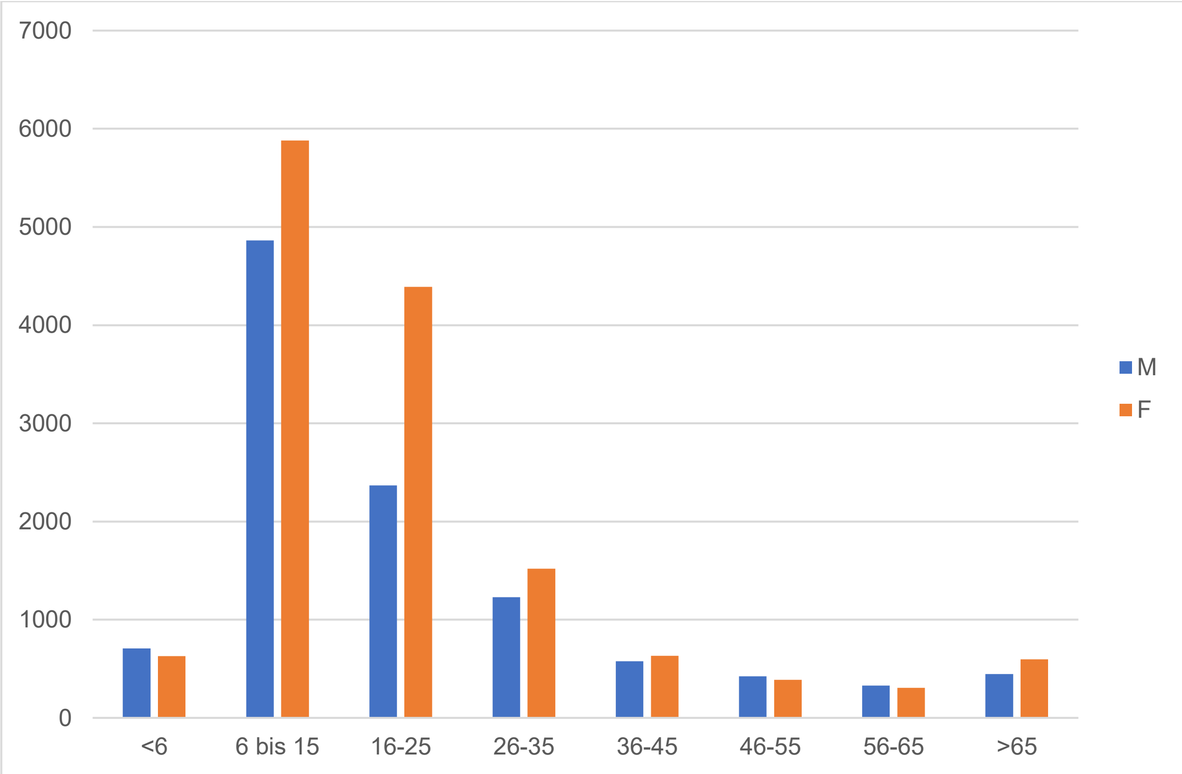

Figure 20: Absolute numbers of appendectomy specimens of females and males related to patient age in the first decade (1987-1996) in the study cohort.

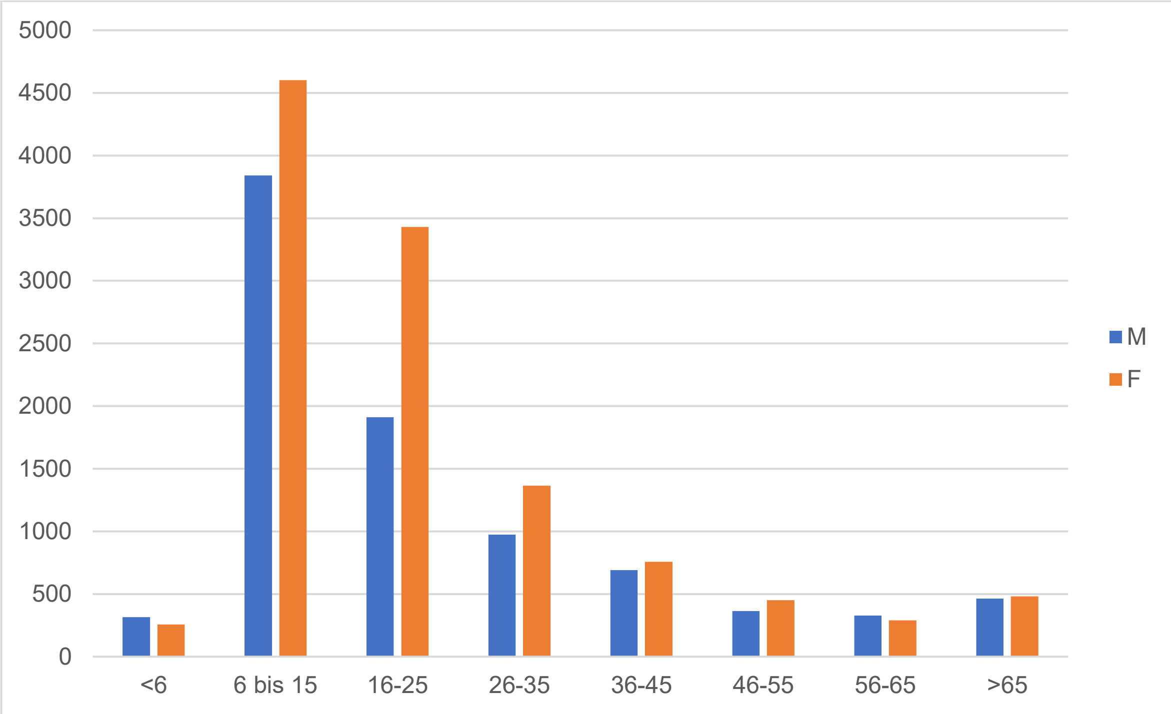

Figure 21: Absolute numbers of appendectomy specimens of females and males related to patient age in the second decade (1997-2006) in the study cohort.

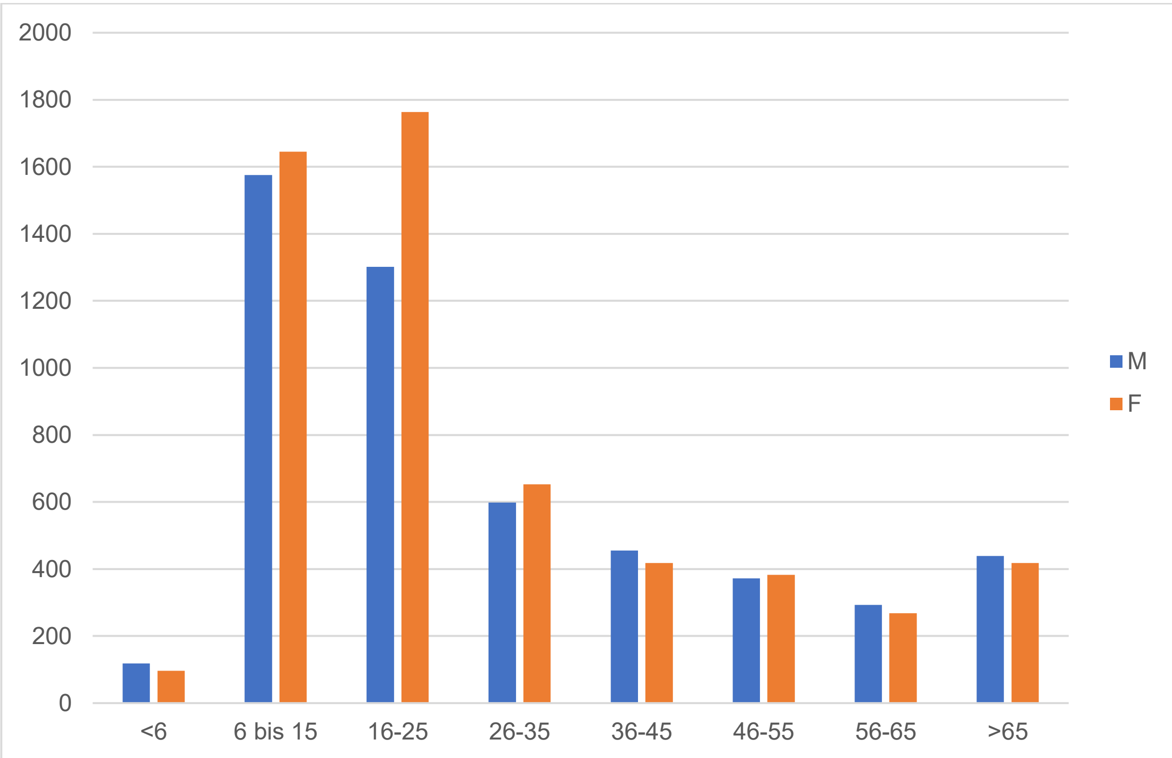

Figure 22: Absolute numbers of appendectomy specimens of females and males related to patient age in the third decade (2007-2016) in the study cohort.

Table 5: Absolute numbers and female/male ratios of appendectomy specimens related to patient age in the first decade (1987-1996) in the study cohort.

Age group	Female	Male	Ratio F/M
<6	629	707	0.89:1
6-15	5,881	4,863	1.21:1
16-25	4,390	2,369	1.85:1
26-35	1,519	1,228	1.24:1
36-45	633	578	1.10:1
46-55	387	425	0.91:1
56-65	306	329	0.93:1
>65	598	446	1.34:1

Table 6: Absolute numbers and female/male ratios of appendectomy specimens related to patient age in the second decade (1997-2006) in the study cohort.

Age group	Female	Male	Ratio F/M
<6	257	316	0.81:1
6-15	4,603	3,842	1.20:1
16-25	3,431	1,912	1.79:1
26-35	1,365	974	1.40:1
36-45	758	691	1.10:1
46-55	452	363	1.25:1
56-65	289	328	0.88:1
>65	482	464	1.04:1

Table 7: Absolute numbers and female/male ratios of appendectomy specimens related to patient age in the third decade (2007-2016) in the study cohort.

Age group	Female	Male	Ratio F/M
<6	96	118	0.81:1
6-15	1,645	1,575	1.04:1
16-25	1,763	1,302	1.35:1
26-35	653	598	1.09:1
36-45	418	455	0.92:1
46-55	383	372	1.03:1
56-65	268	293	0.91:1
>65	418	439	0.95:1

Decrease of female/male ratio was most prominent in the age groups of 6-15 years (female/male ratio = 1.21:1 in 1987 and 0.89:1 in 2016), 16-25 years (female/male ratio = 1.81:1 in 1987 and 1.37:1 in 2016) and 26-35 years (female/male ratio = 1.09:1 in 1987 and 1.21:1 in 2016).

Female/male ratio showed a more stable course in the age groups <6 years (female/male ratio = 0.67:1 in 1987 and 0.58:1 in 2016), 36-45 years (female/male ratio = 1.1:1 in 1987 and 0.6:1 in 2016), 46-55 years (female/male ratio = 1.29:1 in 1987 and 1.11:1 in 2016), 56-65 years (female/male ratio = 1.03:1 in 1987 and 1.05:1 in 2016) and >65 years (female/male ratio = 1.91:1 in 1987 and 0.63:1 in 2016) during the study period.

The following graphs present the development of absolute numbers of appendectomy specimens of females and males during the whole study period for all eight age groups separately. (Figure 23, Figure 24, Figure 25, Figure 26, Figure 27, Figure 28, Figure 29, Figure 30)

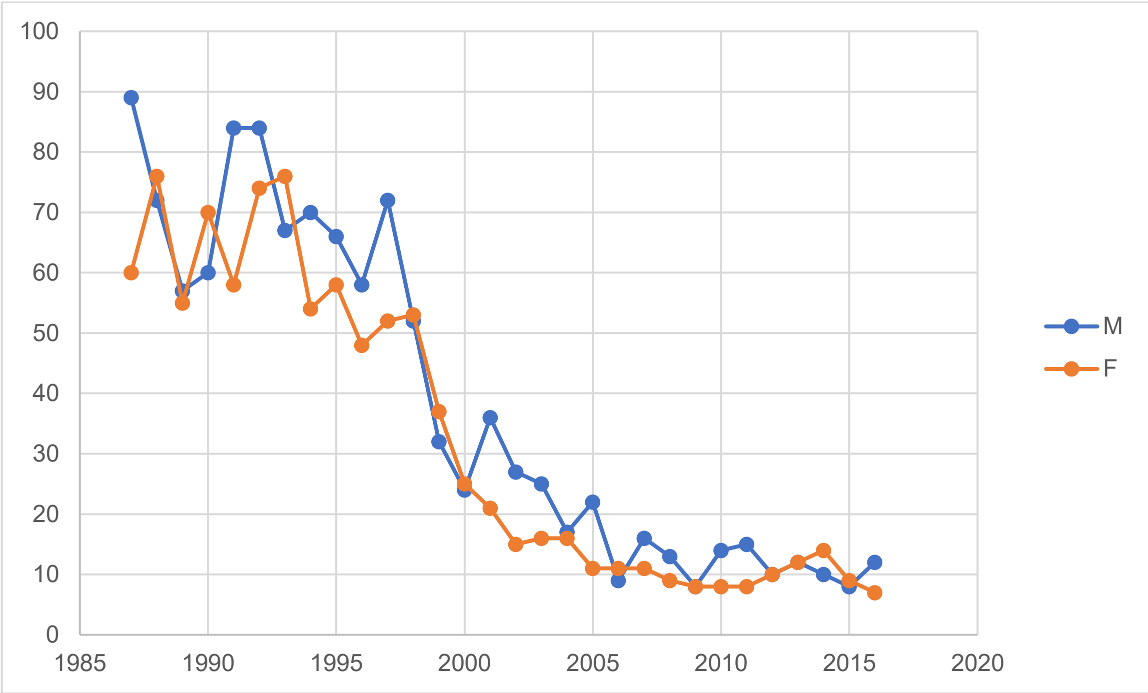

Figure 23: Absolute numbers of appendectomy specimens in the age group <6 years (shown for males and females separately) during the study period.

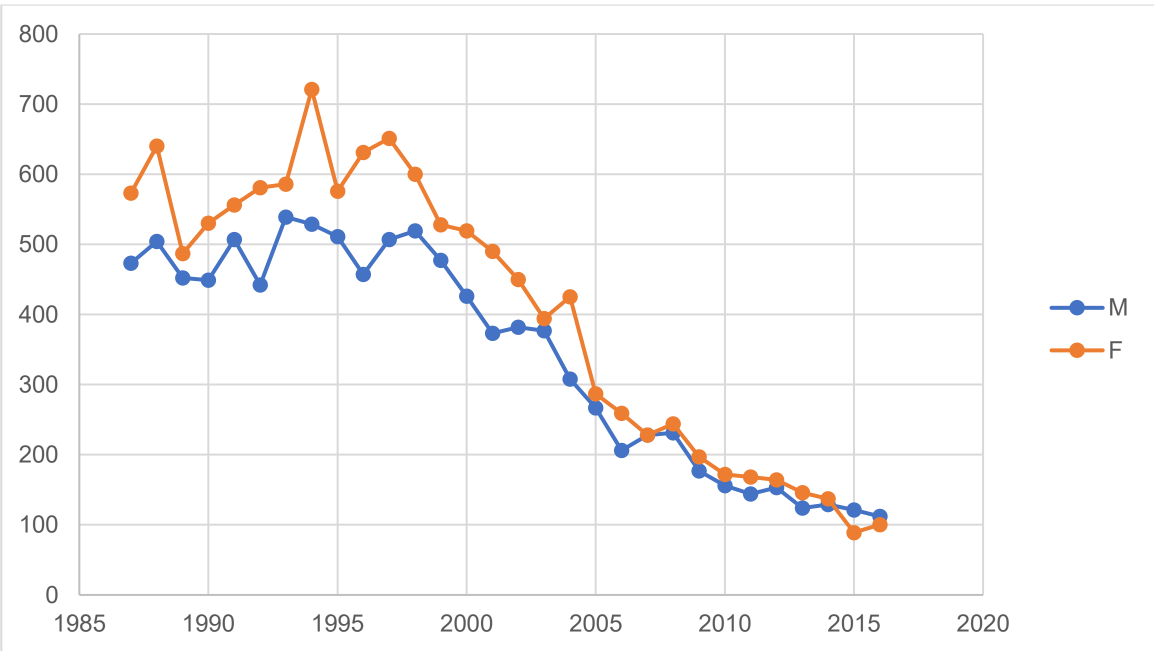

Figure 24: Absolute numbers of appendectomy specimens in the age group 6-15 years (shown for males and females separately) during the study period.

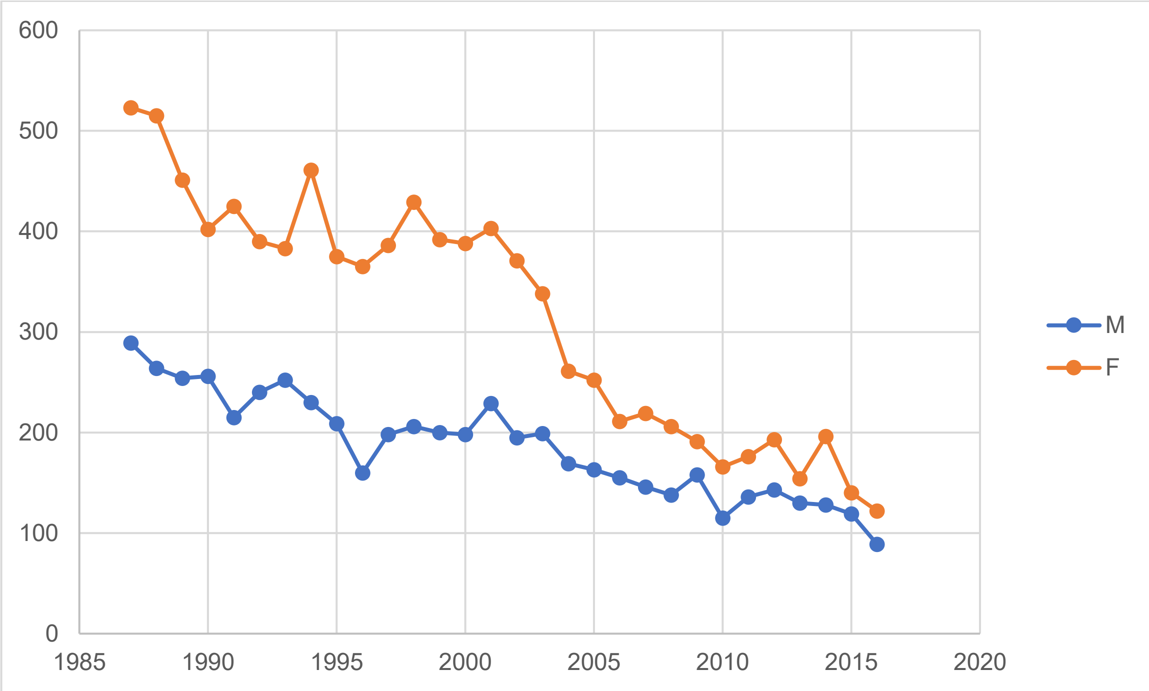

Figure 25: Absolute numbers of appendectomy specimens in the age group 16-25 years (shown for males and females separately) during the study period.

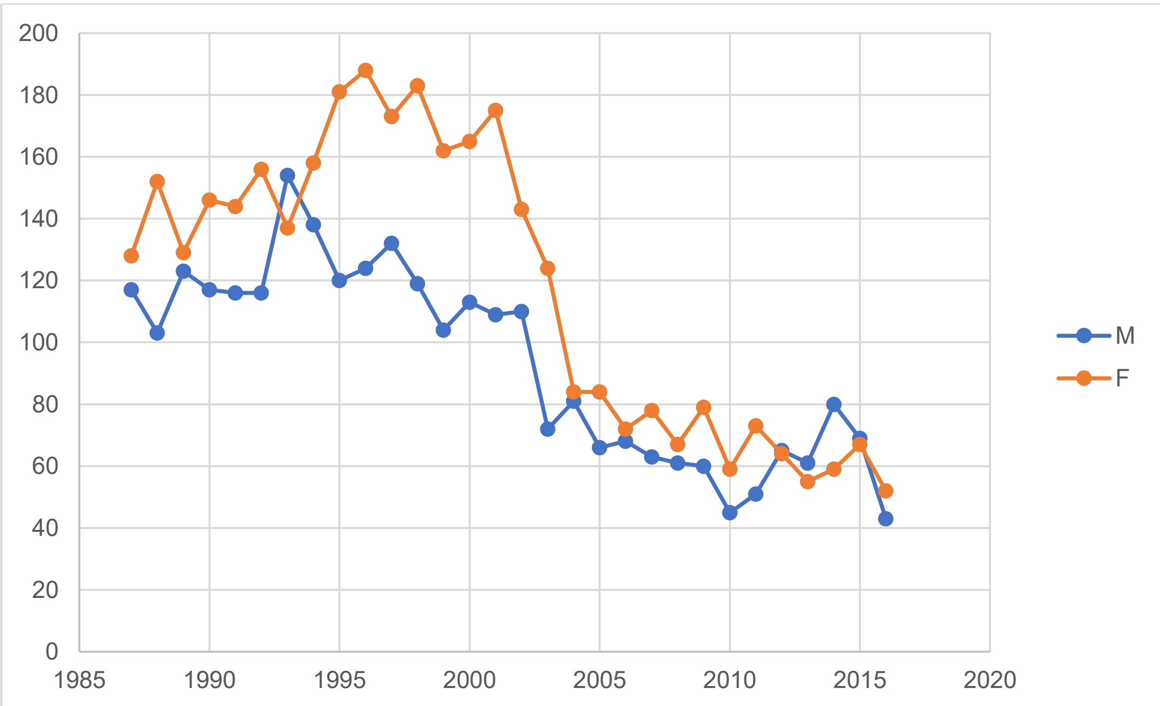

Figure 26: Absolute numbers of appendectomy specimens in the age group 26-35 years (shown for males and females separately) during the study period.

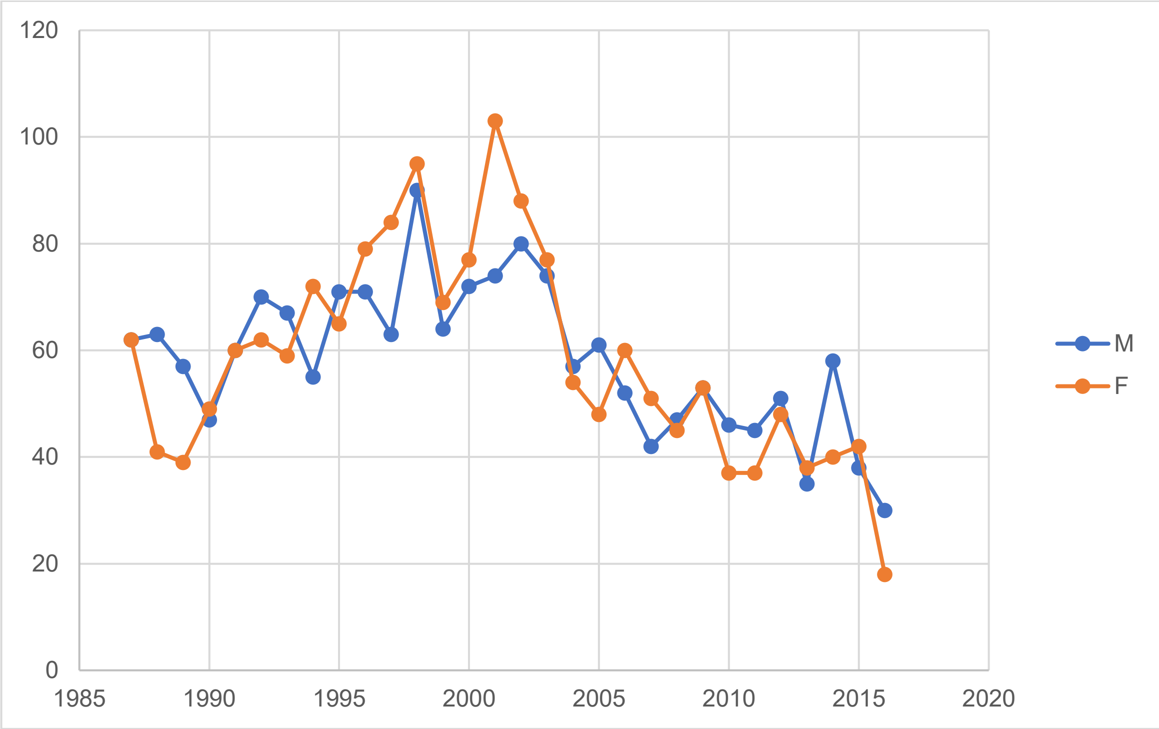

Figure 27: Absolute numbers of appendectomy specimens in the age group 36-45 years (shown for males and females separately) during the study period.

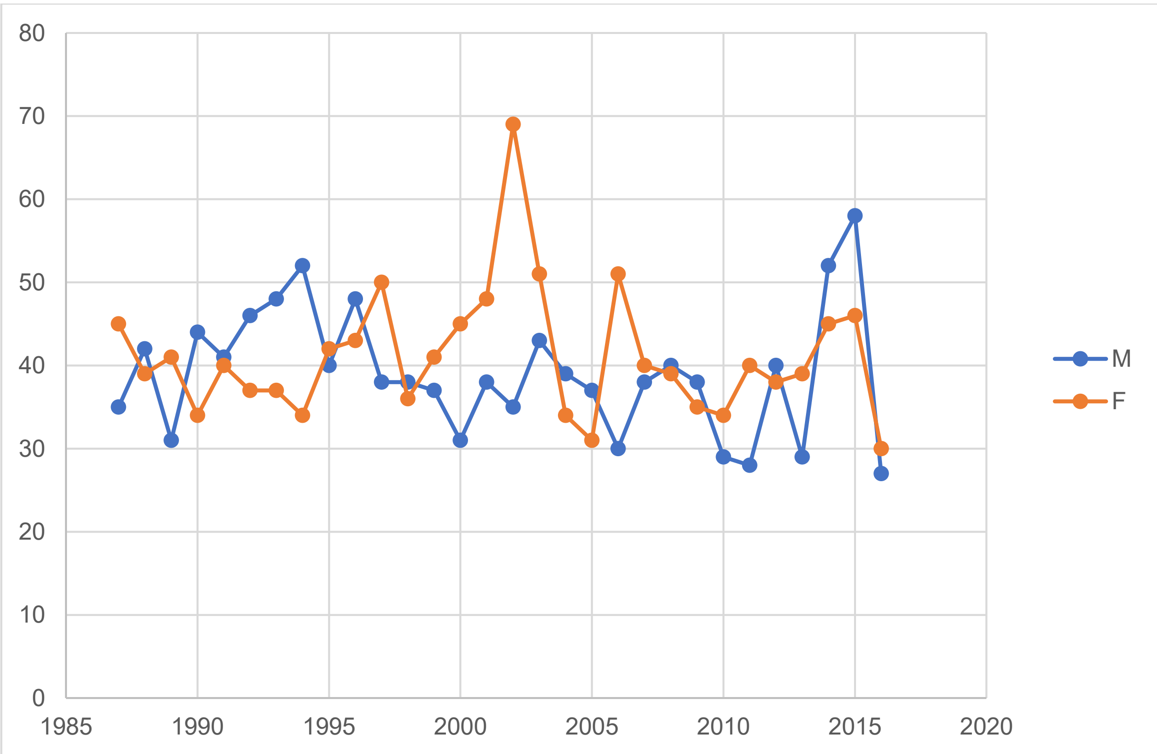

Figure 28: Absolute numbers of appendectomy specimens in the age group 46-55 years (shown for males and females separately) during the study period.

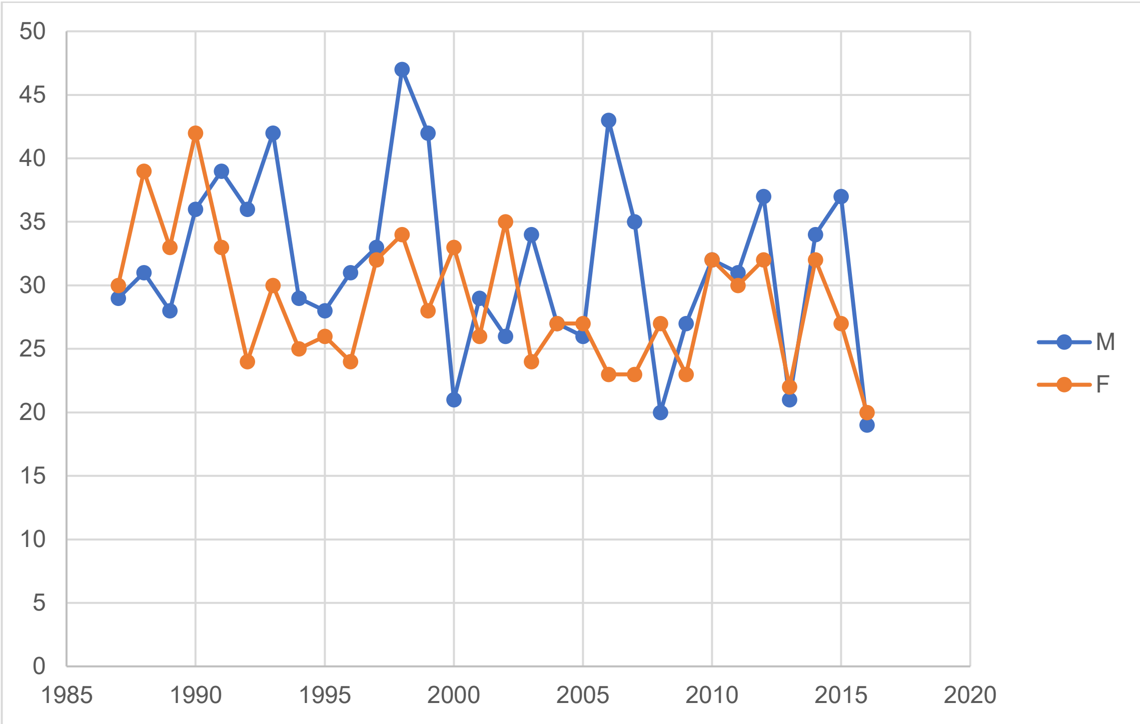

Figure 29: Absolute numbers of appendectomy specimens in the age group 56-65 years (shown for males and females separately) during the study period.

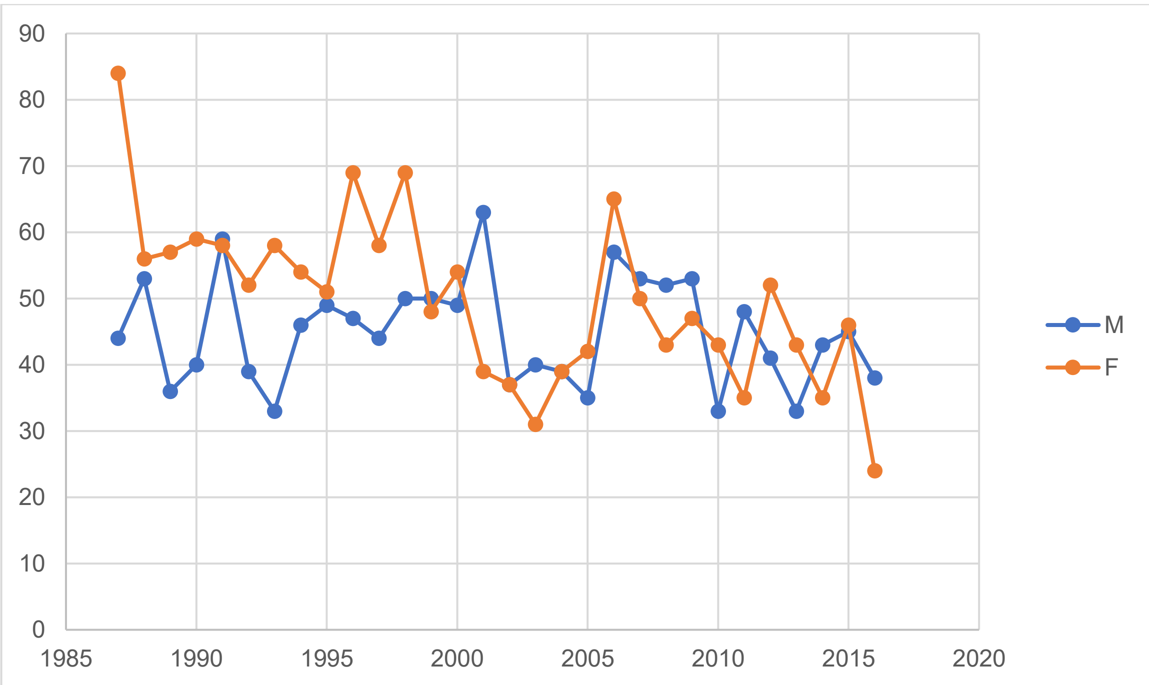

Figure 30: Absolute numbers of appendectomy specimens in the age group >65 years (shown for males and females separately) during the study period.

Analysis of nationwide appendectomy data

The female/male ratio of performed appendectomies in Austria showed a significant ($p<0.001$) decrease from 1997 (female/male ratio = 1.32:1 with 12,323 females and 9,303 males) to 2016 (female/male ratio = 0.98:1 with 6,270 females and 6,398 males). (Figure 31, Figure 32)

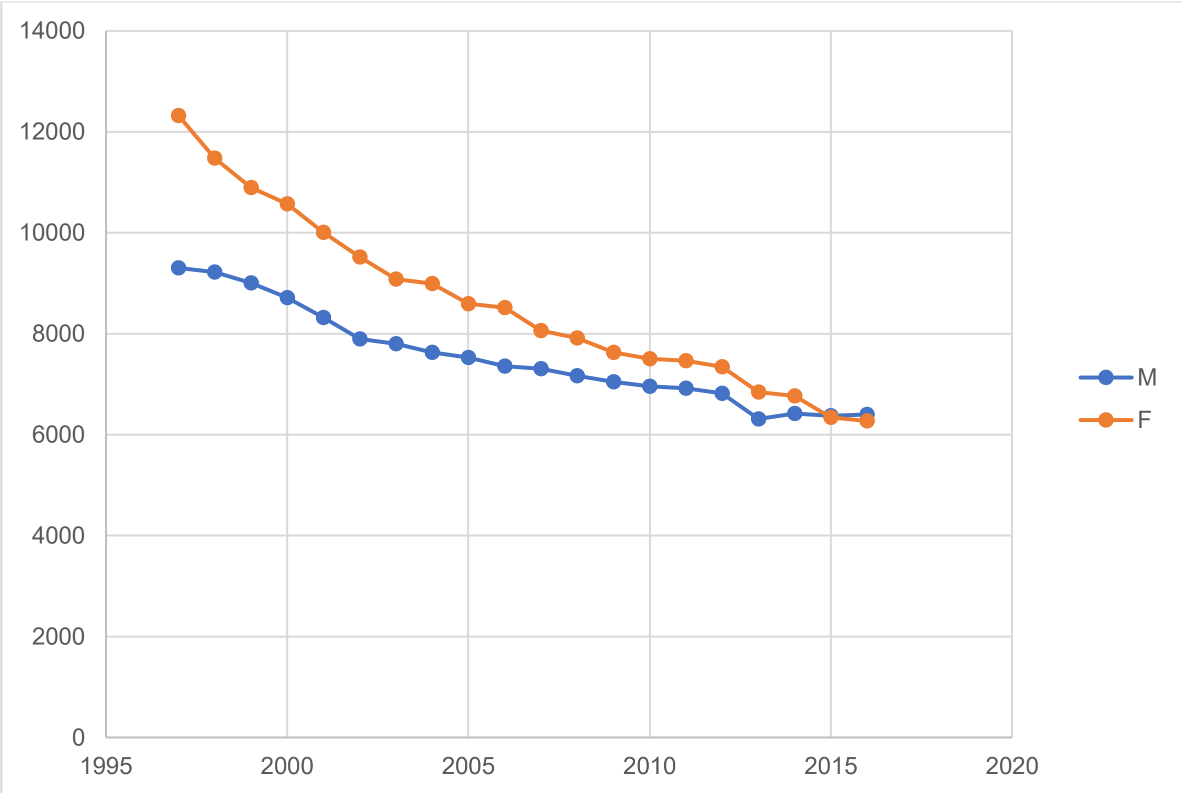

Figure 31: Absolute numbers of appendectomies in Austria (shown for females and males separately) from 1997 to 2016. (Data from Statistics Austria)

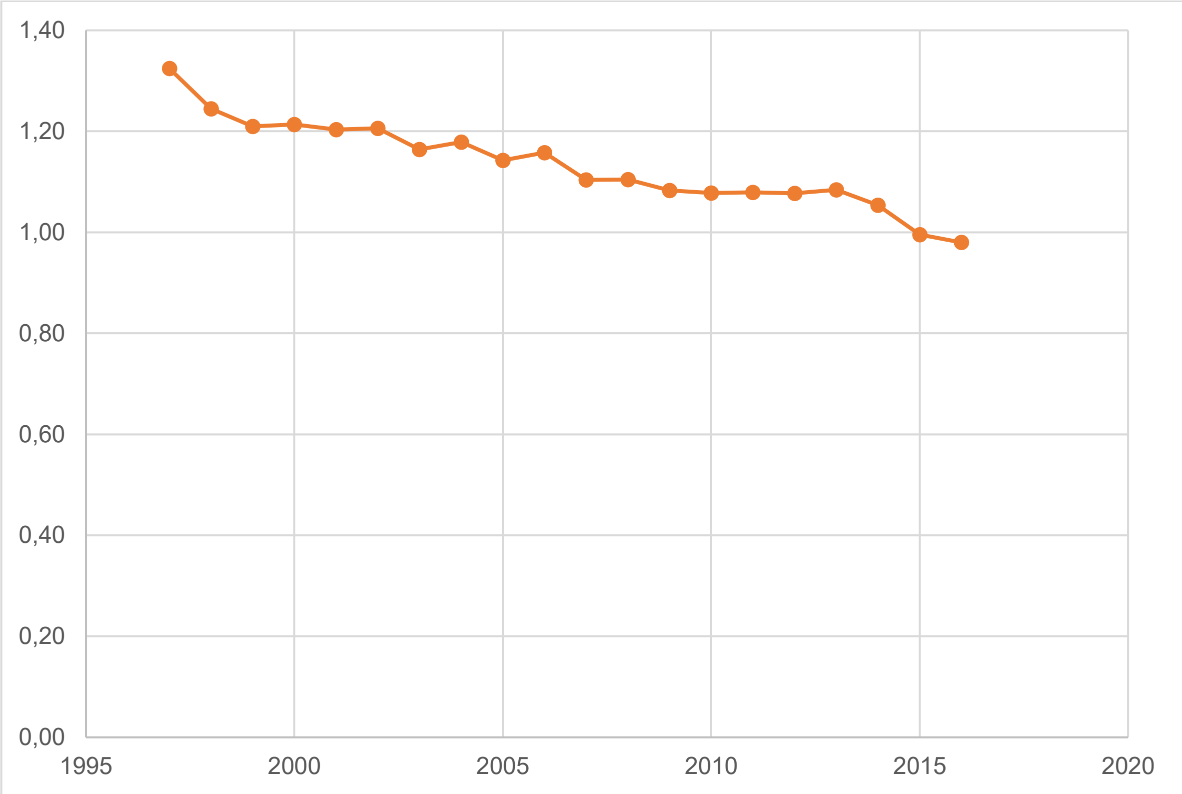

Figure 32: Nationwide development of female/male ratio from 1997 to 2016. (Data from Statistics Austria)

Analyses of histopathological diagnoses

Appendectomy specimens of females were significantly ($p<0.001$) more often diagnosed with no or low-grade inflammation than appendectomy specimens of males. Appendectomy specimens of females were diagnosed in 58.4% with no or low-grade inflammation and in 41.6% with high-grade inflammation. Appendectomy specimens of males were diagnosed in 26% with no or low-grade inflammation and in 74% with high-grade inflammation. (Figure 33, Figure 34)

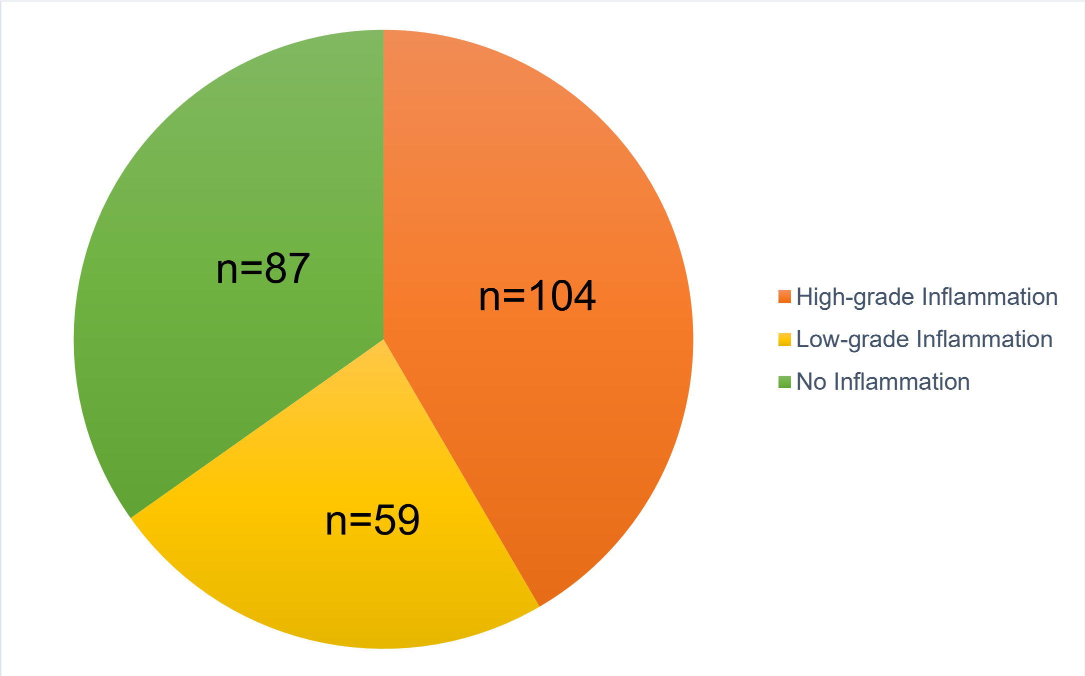

Figure 33: Histopathological diagnoses of appendectomy specimens of females (randomly chosen) in the study period.

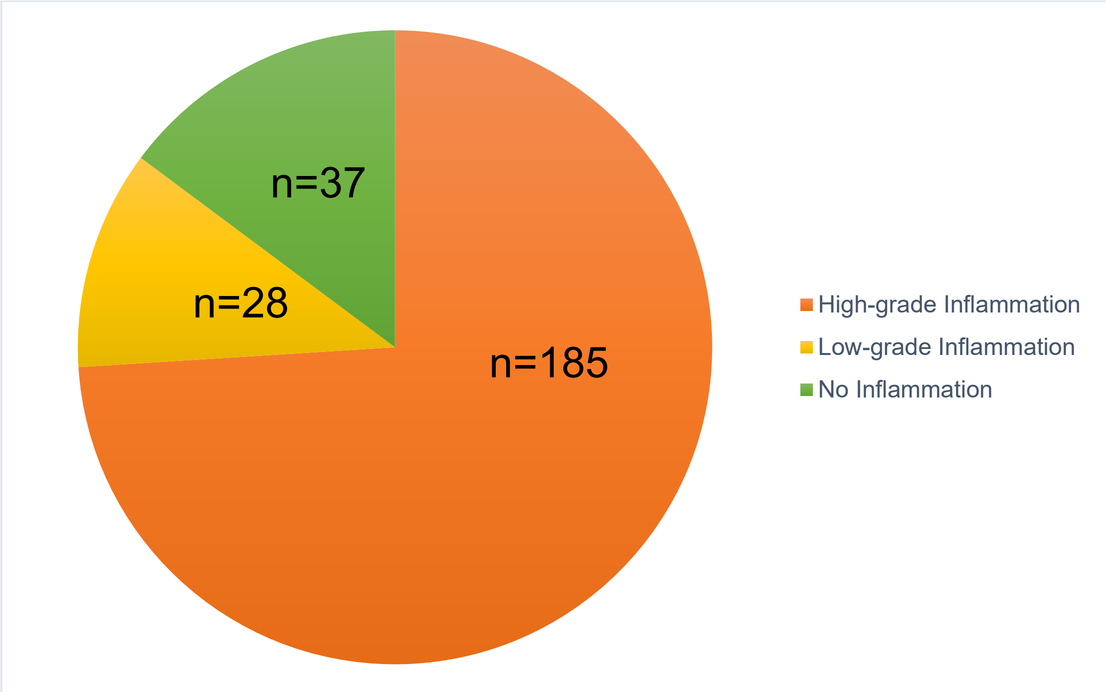

Figure 34: Histopathological diagnoses of appendectomy specimens of males (randomly chosen) in the study period.

The number of appendectomy specimens diagnosed with no or low-grade inflammation decreased during the study period stronger in males than in females (p=0.38). In females, it decreased from 58% in the first decade and 61% in the second decade to 47% in the third decade. In males, it decreased from 43% in the first decade and 44% in the second decade to 23% in the third decade. (Figure 35 Figure 36, Figure 37)

In female patients, the number of appendectomy specimens diagnosed with no acute inflammation decreased by 24% from the first to the third decade, whereas the number of appendectomy specimens diagnosed with high-grade inflammation increased by 26%.

In male patients, the number of appendectomy specimens diagnosed with no acute inflammation decreased by 43% from the first to the third decade, whereas the number of appendectomy specimens diagnosed with high-grade inflammation increased by 35%.

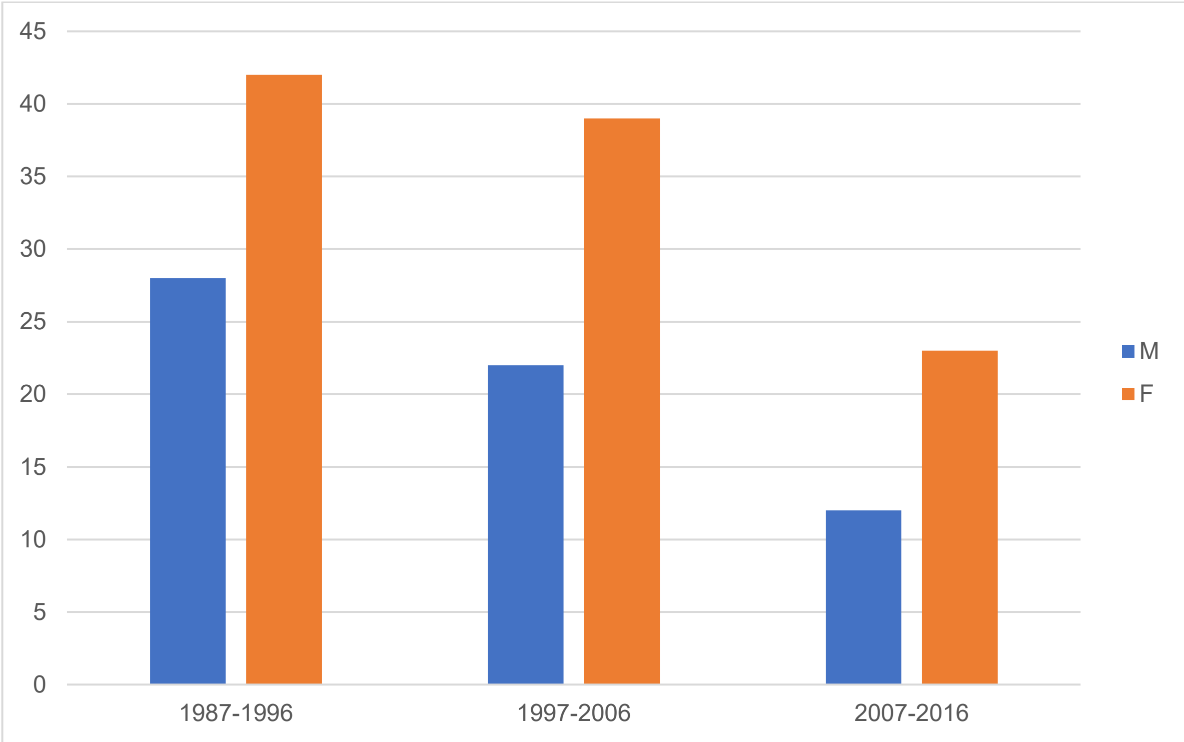

Figure 35: Absolute numbers of appendectomy specimens diagnosed with no acute inflammation of females and males (randomly chosen) shown for all three decades separately.

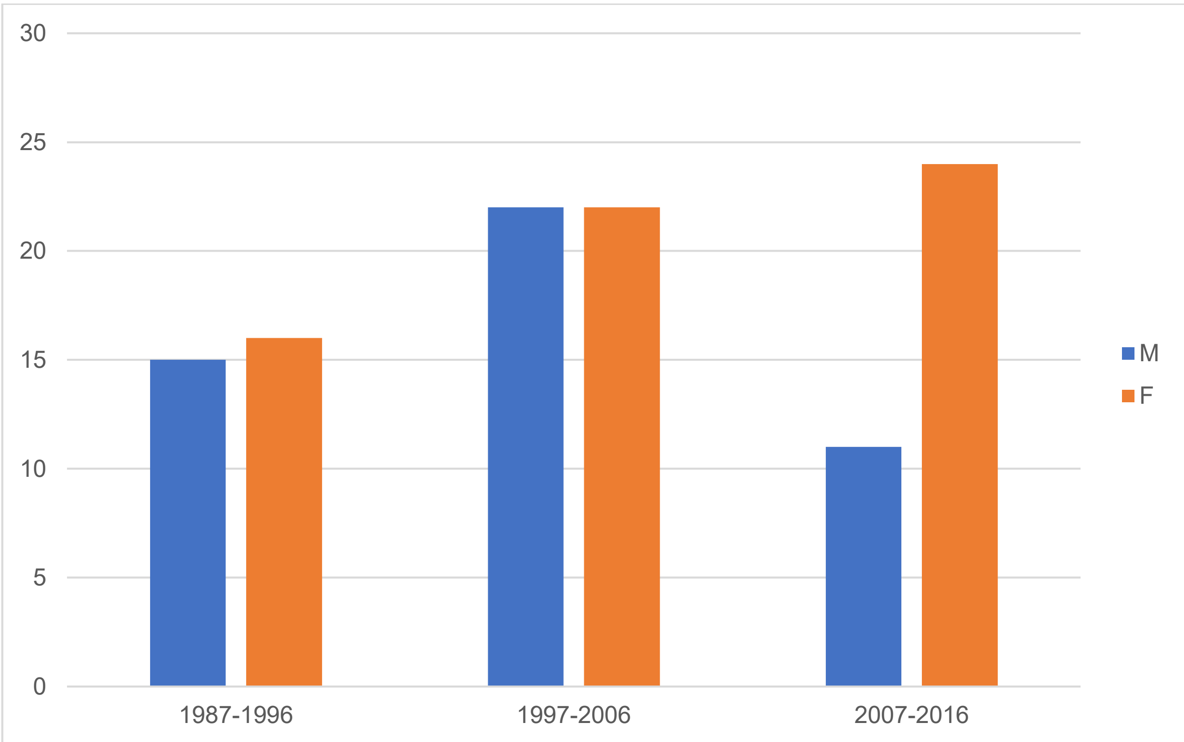

Figure 36: Absolute numbers of appendectomy specimens diagnosed with low-grade inflammation of females and males (randomly chosen) shown for all three decades separately.

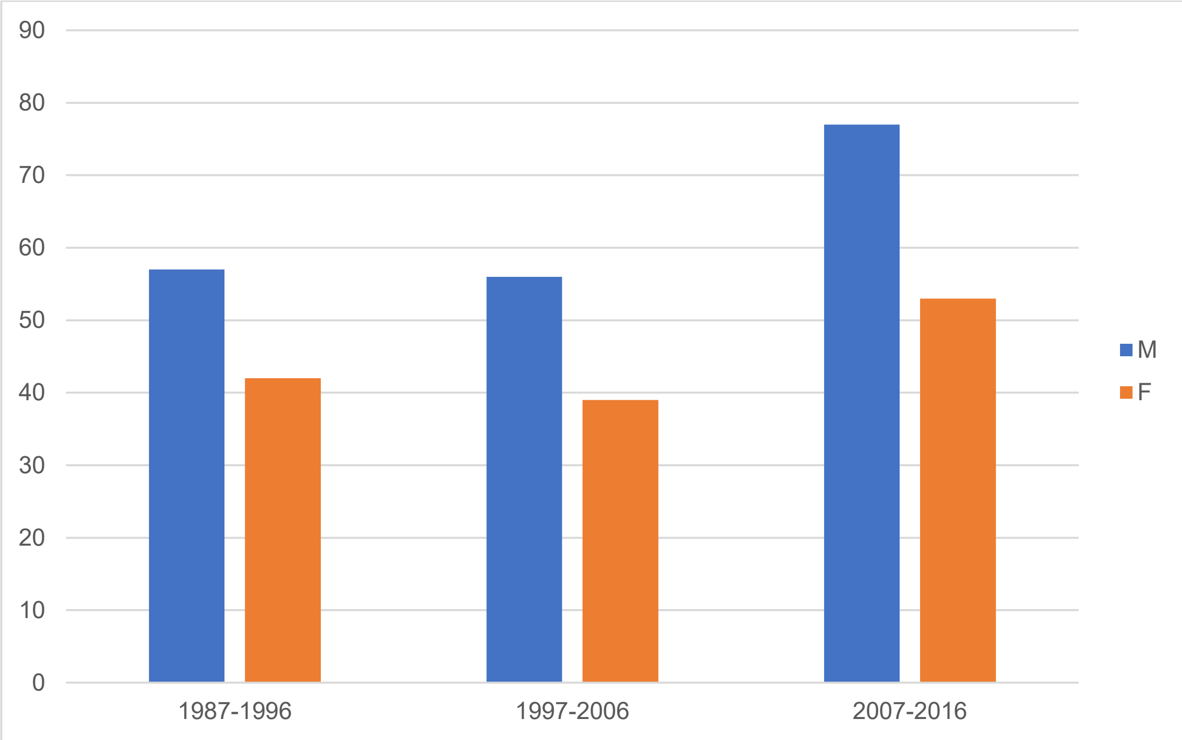

Figure 37: Absolute numbers of appendectomy specimens diagnosed with high-grade inflammation of females and males (randomly chosen) shown for all three decades separately.

Discussion

Even though appendicitis is one of the most common intra-abdominal diseases with a life-time risk of 7%-9% for both genders (14) and appendectomy is one of the most common surgeries performed, the pathogenesis is not yet fully understood, and exact diagnostics remains a challenge in clinical everyday life. (19-22) Literature data show a remarkable decrease in incidence in the past decades in the western world. (1-4) Appendectomy continues to be the gold-standard of treatment with more than 90% of patients undergoing surgery to avoid life-threatening complications like perforation or peritonitis. (43)

Negative appendectomy (defined as appendectomy without pathological findings in the resected appendix) is performed in 15%-25% of patients who undergo appendectomy for suspected acute appendicitis. (44) For females, negative appendectomy rate was reported to be as high as 42%. (45) There has been evidence that negative appendectomy is correlating with increased peri- and postoperative complication risk and longer length of hospitalisation time, (46, 47) other studies suggest that there is no difference regarding complications in resected inflamed and non-inflamed appendices. (48) Several studies show a higher rate of negative appendectomies in females than in males. (14, 45, 46, 48) Addiss et al. found that the life-time risk to suffer from acute appendicitis of children younger than five years is 8.7% for males and 6.7% for females. However, the lifetime risk of undergoing appendectomy is 12.0% for males and 23.1% for females. (14)

Referring to the outcomes in our study population as well as to Literature data, (14, 45-48) it seems justified to assume that the topic of gender-specific difference in (negative) appendectomy rate is an issue of gender-specific medicine. Gender-specific medicine is, by definition, the study of how diseases differ between the genders regarding prevention, clinical features, therapeutic approach, prognosis, and psychological and social impact. (49)

In our study, we analysed the reports of appendectomy specimens diagnosed at the Institute of Pathology at the Medical University of Graz in the period from 1987 to 2016 regarding gender and age. We recognized that the gender difference was significantly most prominent in the first decade of the study period and in the age group of 16-25 years. These findings are in line with Literature data describing higher numbers of appendectomies in females than in males in the second half of the 20th century.

As far back as in the 1960s the gender difference of performed appendectomies was noted. In 1961, Lee et al. found higher numbers of appendectomies performed on females, especially at the age around 17, than on males who had their age peak at around 12 years. Even then, they guessed that the high appendectomy rate of women between 14 and 26 was due to gynaecological issues, though availability of data and infrastructure was not sufficient to investigate exact (negative) appendectomy rates. (50)

In the 1980s, Nakhgevany et al. examined negative appendectomy rates in females. They described an incidence of 59% for women at the age of 15 to 25 years to undergo negative appendectomy compared to an incidence of 22% for women aged 36 to 45 years. More than half of the women without pathological findings in the resected appendices suffered from pelvic inflammatory disease or ovarian abnormalities. (50) Due to these findings, Nakhgevany et al. as well as Lee at al. recommended observation and frequent clinical examinations, but more important, additional examination of female patients by a gynaecologist. (50, 51)

In the 1990s, Addiss et al. detected a higher negative appendectomy rate in females than in males, especially in women of childbearing age with more than twice as many negative appendectomies performed on than on men. Simultaneously, diagnostic accuracy was detected to be higher in men. (14)

Although the greatest gender difference in our data was observed in women of childbearing age (between 16 and 25 years), girls between 6 and 15 years underwent appendectomy more often than boys of the same age (female/male ratio 1.18:1). In children younger than 6 years the ratio showed the exact opposite. In literature there has been described a higher rate of negative appendectomies in girls than in boys in children younger than 15 years as well. Though negative appendectomies are mostly an issue in women of childbearing age, younger girls are affected too. (52)

In our study, we see not only that females were more likely to undergo appendectomy than males, but also to get histopathologically diagnosed twice as often as males with no inflammation or low-grade inflammation. The most obvious reason for this gender difference is the fact that gynaecological issues are anatomically predestined to mimic the symptoms of acute appendicitis.

In literature, models for differentiation of these two disease patterns were proposed. Webster et al. found a significantly higher number of anorexia in patients with acute appendicitis and a significantly higher number of tenderness outside the lower right abdominal quadrant as well as cervical motion tenderness in patients with pelvic inflammatory disease. Furthermore, history of prior pelvic inflammatory disease was a crucial factor in diagnostic work-up. There has not been reported any difference regarding the occurrence of nausea and vomiting. (53) Lewis et al. noted that presence of anorexia, nausea and vomiting and duration of symptoms less than one day were more common in patients with acute appendicitis, whereas duration of symptoms more than two days and a period of less than seven days since the last onset of menstrual period were more common in patients with pelvic inflammatory disease. (54) A more recent study suggested three clinical features that exclude acute appendicitis in women presenting with acute abdominal pain: No migration of pain, presence of bilateral abdominal pain and absence of nausea and vomiting. (55)

Yet, clinical diagnosis of acute appendicitis had remained a challenge, especially for women of childbearing age. Despite the decreasing appendectomy rates since the 1950s, (1-4, 14) only recent studies could note a significant decrease in negative appendectomy rate. Several studies performed in different nations have described a decrease due to the diagnostic usage of computed tomography.

The Netherlands implemented new guidelines of diagnosing acute appendicitis in 2010. These guidelines mainly included the standardized use of sonography and/or computed tomography. Subsequently, Hendriks et al. noted a decrease of negative appendectomies from 18% to 9%, (56) Boonstra et al. even noted a decrease from 19% to 5%. (57)

Jones et al. described a decrease of negative appendectomy rate from 17% in 2000 to 9% in 2001 and 2% in 2002 with a simultaneous increase of the usage of preoperative computed tomography scans. (58) Wagner et al. found that the overall rate of negative appendectomies decreased from 10.6% in 2000 to 5.0% in 2006. In addition, a lower rate of negative appendectomies in cases diagnosed with computed tomography was observed. (59) Raja et al. described a decrease of negative appendectomies from 23% in 1990 to 1.7% in 2007 at the Harvard Medical School. (60) Kim et al. compared two groups of patients with suspected acute appendicitis. The group diagnosed with computed tomography showed a significantly lower negative appendectomy rate. (38) Raman et al. found a significant inverse relationship between the increased use of computed tomography and the decrease of false positive diagnosis of acute appendicitis. (37)

Moreover, Coursey et al. found that the usage of preoperative CT decreased the number of negative appendectomies only in women younger than 45 years old, but not in men any age. Also, the CT technology played a role in the lower number of negative appendectomies: The use of multidetector CT instead of single-detector CT and the use of decreasing section thickness were shown to be positive factors. (61)

These outcomes lead to the assumption that the adjustment of the gender difference in our cohort and the reduction of negative appendectomy rate in the mentioned studies are caused by similar reasons. The female/male ratio in Austria as well as in our study cohort adjusted from 4:3 in 1997 to 1:1 in 2016. According to our data, women were histopathologically diagnosed more often with no or low-grade inflammation of the appendix. Also, the number of diagnosed “no acute or low-grade inflammation” specimens decreased in both genders throughout the study period. Considering these factors, there is strong probability that the reported adjustment of the gender difference in our study cohort as well as in Austria is due to improved diagnostic techniques, especially to the increased use of computed tomography.

But there also has been doubt in the important diagnostic role of computed tomography. Flum et al. could not report a decrease in misdiagnosing acute appendicitis during the period from 1987 to 1998 despite the increased use of advanced diagnostic tools like computed tomography, laparoscopy and sonography. (62) Frei et al. did report a slight but not statistically significant decrease in negative appendectomies, due to false positive CT scans and cases of performed surgeries despite negative CT scans. (63) In addition, the radiation-induced cancer risk of routine computed tomography scans should not be underestimated. (64)

Even though there are studies which cannot find a correlation between improved imaging diagnostics and the decrease of negative appendectomy rate, (62, 63) many other studies found that correlation. (37, 38, 56-60) As mentioned before, in our study population, the greatest gender difference and adjustment of gender difference was observed in the age group 16-25 years. So, it is to be assumed that the improved imaging diagnostics affects this group the most. However, Antevil et al. found a decrease in negative appendectomies due to increased use of computed tomography, but only in older patients (>30) and only in females. They did not find any advantage in using computed tomography for younger patients (<30). They suggest preoperative CT scans for females. (45)

Some studies suggest diagnostic laparoscopy instead of computed tomography for diagnosing acute appendicitis and differentiating acute appendicitis from intrapelvic pathologies in females of childbearing age. Garbarino et al. found a reduction in negative appendectomy rate from 37% to 5% among young female patients using diagnostic laparoscopy routinely. However, the use of selective laparoscopy did not lead to a significant reduction of negative appendectomy rate. They suggest routinely usage of diagnostic laparoscopy for young women. (65) Lim et al. also found that women of childbearing age benefit the most from this procedure. (66)

Our study has an important limitation. Our data did not allow exact analysis regarding the development of absolute appendectomy numbers over time in Southern Austria due to structural changes in the commuting area of the Institute of Pathology at the Medical University in Graz during the study period. Therefore, the main focus of our study is on the analysis of female/male ratios.

In conclusion, we were able to show the adjustment of gender difference of appendectomies in a time span of 30 years up to almost balancing ratios as well as a decrease in the number of histopathologically confirmed resected appendices without or with only low-grade inflammation. These outcomes reflect the results of Literature data, in which a decrease of negative appendectomies in the past decade mainly due to improved diagnostic imaging tools is described.

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