

VIII. STRESZCZENIE W JĘZYKU ANGIELSKIM.

INTRODUCTION

The appendix is a blindly terminated tube branching off from the cecum, with an average length of 8 cm. Morphologically, acute appendicitis occurs as uncomplicated appendicitis and complicated appendicitis. Nonperforated appendicitis includes catarrhal appendicitis and phlegmonous appendicitis. Conversely, perforated appendicitis occurs as: gangrenous appendicitis, perforated appendicitis, gangrenous appendicitis with diffuse peritonitis as well as gangrenous appendicitis with intraabdominal abscess.

The treatment of choice for acute appendicitis (both non-complicated and complicated) is surgical intervention. Such a procedure carries the risk of early postoperative complications, typical of appendectomy, including: surgical site infection, septic complications mostly intra-abdominal abscesses, small bowel obstruction, hemorrhagic complications, and in rare cases, the occurrence of an intestinal/fecal fistula.

AIM

The aim of the doctoral thesis was:

1. To assess the number of patients with complicated appendicitis hospitalized in the Department of General, Minimally Invasive, and Oncological Surgery at the Wojewodzki Szpital Zespólny in Białystok between 1999-2003, and 2014-2018.
2. To characterize the demographic data, i.e. the age and gender, of patients hospitalized due to complicated appendicitis in the Department of General, Minimally Invasive, and Oncological Surgery at the Wojewodzki Szpital Zespólny in Białystok between 1999-2003, and 2014-2018.
3. To evaluate the trend in the relationship between the age group of operated patients and the frequency of complicated appendicitis occurrence.
4. To assess the data regarding the hospitalization course of patients with complicated appendicitis, including the time from symptom onset to hospital admission, pain migration, nausea/vomiting, elevated temperature, body mass index (BMI), tenderness in right iliac fossa, rebound tenderness, leukocytosis, neutrophils above 75%, Alvarado score (in points), ASA grade, time from patient's department admission to the performance of the surgical procedure, method of appendectomy, duration of appendectomy, and the stage of complicated appendicitis in patients hospitalized between 1999-2003, and 2014-2018.

5. To assess the number and types of complicated appendicitis cases in patients hospitalized between 1999-2003 and 2014-2018.

6. To evaluate the variations in the position of the appendix in patients hospitalized between 1999-2003 and 2014-2018 as well as its impact on the particular stage of complicated appendicitis.

7. To evaluate the number of post-appendectomy reoperations, length of hospitalization, extended hospitalization, and mortality rate among patients hospitalized due to complicated appendicitis between 1999-2003 and 2014-2018.

8. To evaluate the risk factors for the occurrence of complicated appendicitis using logistic regression modelling.

9. To assess the number and types of early postoperative complications among patients hospitalized due to complicated appendicitis between 1999-2003 and 2014-2018.

10. To characterize the demographic data, i.e. age and gender of patients hospitalized due to complicated appendicitis between 1999-2003 and 2014-2018 who experienced early postoperative complications.

11. To assess the risk factors for extended hospitalization among patients who underwent surgery for complicated appendicitis between 1999-2003 and 2014-2018.

MATERIAL AND METHOD

The thesis included a retrospective analysis of medical records of patients who underwent surgery for complicated appendicitis between the years 1999-2003 and 2014-2018. The period from 1999-2003 was designated as period I, while the period from 2014-2018 was designated as period II. Hospitalisation length exceeding 5 days (for patients who underwent surgery for complicated appendicitis) was defined as prolonged hospitalization. In period I, the department performed surgery on 263 patients with complicated appendicitis, whereas in period II, 226 patients underwent surgery for complicated appendicitis. The analysis also considered early postoperative complications among patients with complicated appendicitis in both period I and period II.

RESULTS

In the current study, during period I (1999-2003), 723 patients with acute appendicitis were hospitalized at the department, while during period II (2014-2018), 578 such patients were hospitalized. Additionally, a significantly higher ($p < 0.006$) proportion of acute appendicitis cases relative to all hospitalizations was observed during period I as compared to

period II. However, the number of patients hospitalized for complicated appendicitis in both periods was similar (263 in period I, 226 in period II), and no statistically significant difference was observed in the percentage of these hospitalizations compared to the number of patients hospitalized due to acute appendicitis.

In period II, the mean age of patients hospitalized for complicated appendicitis was 45.70 ± 18.356 years, which was significantly higher ($p < 0.001$) than the mean age of patients hospitalized in period I (39.96 ± 18.782 years). Furthermore, a statistically significant trend was observed between the age group of operated patients and the frequency of occurrence of complicated appendicitis ($p < 0.001$). As age increased, a higher percentage of patients with complicated appendicitis was observed. In the case of patients aged 61-75, it was found that there was a significantly higher rate ($p = 0.013$) of patients with complicated appendicitis in period II (72%) as compared to period I (51%).

In the present study, a higher occurrence of complicated appendicitis was observed among males compared to females, with a female-to-male ratio of 1;1,26 in period I and 1;1,09 in period II.

The study also found a statistically significant difference ($p = 0.004$) in the time elapsed from the onset of symptoms related to complicated appendicitis to seeking medical care between period I (37.67 ± 36.63 hours) and period II (51.31 ± 101.09 hours).

The obtained results indicate that a statistically significant ($p < 0.001$) lower percentage of patients operated on for complicated appendicitis in period I reported pain migration (25.9%) as compared period II (43.8%). Similarly, in period I, a statistically significant ($p = 0.005$) lower percentage of patients with complicated appendicitis (26.2%) reported loss of appetite compared to period II (38.5%). However, there was no statistically significant difference between the two periods regarding nausea and vomiting reported by patients. The statistical analysis revealed that a statistically significant ($p < 0.001$) lower percentage of patients in period II (14.2%) reported elevated body temperature ($\geq 37.3^\circ\text{C}$) compared to the percentage of patients in period I (47.5%) who reported this symptom.

The conducted study found that patients with complicated appendicitis operated on in period I had a lower prevalence of overweight as compared to those operated in period II. In period I, a statistically significant ($p = 0.001$). lower BMI of 24.80 ± 4.44 (median 24.42) was observed compared to a BMI of 26.60 ± 4.42 (median 26.04) in patients in period II.

Additionally, in period II, there was a statistically significant higher ($p < 0.001$) percentage of patients reporting tenderness in right iliac fossa and a higher percentage of patients with a rebound tenderness during physical examination.

Patients with complicated appendicitis undergo laboratory tests for diagnostic purposes, i.e. the evaluation of leukocyte count and the assessment of neutrophils above 75%. The conducted statistical analysis showed no significant difference ($p = 0.386$) in the percentage of hospitalized patients with complicated appendicitis who had leukocytosis $\geq 10,000/\mu\text{l}$ in period I compared to the percentage of patients with leukocytosis $\geq 10,000/\mu\text{l}$ in period II. However, in period I, a statistically significant higher percentage ($p = 0.045$) of hospitalized patients with complicated appendicitis had neutrophils above 75% compared to those hospitalized in period II.

The statistical analysis revealed that in period I, patients with complicated appendicitis had a significantly ($p < 0.001$) lower number of points on the Alvarado scale: 4.62 ± 1.70 (median 5), compared to patients with complicated appendicitis in period II, 5.31 ± 1.69 (median 5). Patients hospitalized in period II were on average 5.74 years older than patients hospitalized in period I. The conducted study showed that older age in patients is associated with a higher number of points on the Alvarado scale.

Significant statistically differences ($p < 0.001$) were observed in the occurrence of individual classes of the ASA scale between period I and period II. The occurrence of class I in the ASA scale significantly decreased from 70.3% in period I to 43.8% in period II, while simultaneously, there was a significant increase in the occurrence of patients in class II of the ASA scale from 22.1% in period I to 52.2% in period II. There were reductions in the other classes as well: class III of the ASA scale decreased from 6.5% in period I to 4% in period II, and class IV of the ASA scale decreased from 1.1% in period I to 0 in period II (no patients). No significant statistical differences were observed regarding class III and class IV of the ASA scale.

Among patients with complicated appendicitis, the mean time from hospital admission to the surgical procedure was significantly shorter in period I ($p < 0.001$) and amounted to 6.07 ± 16.42 (median 4) hours, whereas in period II, it was 7.16 ± 12.63 (median 4) hours. In period I, all patients with complicated appendicitis were operated on using open appendectomy, while in period II, 7 patients were operated on using open appendectomy and

219 patients were operated on using the laparoscopic appendectomy. The change in the appendectomy surgical method from open to laparoscopic contributed to an increase in the duration of the procedure by 18.33 minutes, from 56.12 ± 25.30 (median 50) minutes in period I to 74.45 ± 25.43 (median 70) minutes in period II, and this difference was statistically significant ($p < 0.001$). Additionally, it was found that the duration of the laparoscopic procedure (performed solely in period II) was longer - 74.7 ± 25.7 (median 70) minutes - compared to the duration of the open appendectomy in period I patients which equalled 56.1 ± 25.3 (median 50) minutes. The performed analysis showed a significant statistical difference in the duration of the surgical procedure between the open and laparoscopic methods ($p < 0.001$).

The study also provided an assessment of the duration of the procedure depending on the severity of complicated appendicitis. Among patients with gangrenous appendicitis, a significant statistical difference ($p < 0.001$) in the duration of the operation was found, which was equal to 47.37 ± 19.420 minutes in period I and an elongated 67.38 ± 21.361 minutes in period II. Similarly, a significant statistical difference ($p = 0.004$) was shown in the duration of the procedure for patients with appendicitis with complicated appendicitis with diffuse peritonitis, with the statistic being equal to 61.67 ± 23.963 minutes in period I and 96.00 ± 30.677 minutes in period II. However, no difference was found in the duration of the procedure for patients with gangrenous appendicitis with perforation ($p = 0.176$) and complicated appendicitis with abscess ($p = 0.412$).

Among patients with acute appendicitis in period I, the following degrees of appendiceal inflammation were identified: 171 (65.5%) patients had a gangrenous appendicitis, 54 (20.7%) patients had a gangrenous appendicitis with perforation, 24 (9.2%) patients had complicated appendicitis with abscess formation and 12 (4.6%) patients had complicated appendicitis with diffuse peritonitis. In period II, there were 120 (53.3%) cases gangrenous appendicitis, 50 (22.2%) cases of gangrenous appendicitis with perforation, and 20 (8.9%) cases of complicated appendicitis with diffuse peritonitis. The analysis showed a statistically significant difference between the two periods ($p = 0.015$).

In period I, a higher percentage of 23.5% (171 patients) with gangrenous appendicitis was observed among patients with acute appendicitis. In contrast, in period II, a lower percentage of 20.8% (120 patients) with gangrenous appendicitis was observed. There was no significant statistical difference between the periods ($p = 0.228$).

In period II, a higher percentage of 8.8% (51) of patients with gangrenous appendicitis with perforation was observed compared to the first period where 7.7% (56) such patients were observed. The conducted analysis showed that this difference was not statistically significant ($p=0.480$).

In period II, a higher percentage of 6.1% (35) patients with complicated appendicitis with abscess formation was observed compared to 3.5% (25) patients in period I. The analysis showed that this difference was statistically significant ($p=0.033$).

In period II, a higher percentage of 3.5% (20) of patients with complicated appendicitis with diffuse peritonitis was observed compared to 1.7% (12) of such patients in period I. The analysis showed that this difference was statistically significant ($p=0.047$).

Among patients with acute appendicitis, a higher percentage of 30.8% (81) had atypical appendiceal positions in period I, compared to 19.5% (44) of patients with atypical appendiceal positions in period II. The analysis showed a significant statistical difference in the occurrence of atypical appendiceal positions between both periods ($p=0.005$).

In period I, during surgery, typical appendiceal positions were found in 124 patients (68.5%) with gangrenous appendicitis, 34 patients (18.8%) with gangrenous appendicitis with perforation, 15 patients (8.3%) with appendicitis with abscess formation, and 8 patients (4.4%) with appendicitis with diffuse peritonitis. In the same first period, atypical appendiceal positions were found in 47 patients (58.5%) with gangrenous appendicitis, 34 patients (18.8%) with gangrenous appendicitis with perforation, 15 patients (8.3%) with appendicitis with abscess formation, and 8 patients (4.4%) with appendicitis with diffuse peritonitis. Differences in the degree of inflammation depending on the appendiceal position were not statistically significant ($p=0.459$). In period II, during surgery, typical appendiceal positions were found in 97 patients (65.5%) with gangrenous appendicitis, 41 patients (22.7%) with gangrenous appendicitis with perforation, 28 patients (15.5%) with appendicitis with abscess formation, and 15 patients (8.3%) with appendicitis with diffuse peritonitis. In the same period (II), atypical appendiceal positions were found in 23 patients (52.3%) with gangrenous appendicitis, 9 patients (20.5%) with gangrenous appendicitis with perforation, 7 patients (15.9%) with appendicitis with abscess formation, and 5 patients (11.4%) with appendicitis with diffuse peritonitis. Differences in the degree of inflammation depending on the appendiceal position were not statistically significant ($p=0.897$).

In period I, there were 9 (3.4%) patient reoperations after appendectomy, while in period II, there were 7 (3.1%) patient reoperations after appendectomy. The statistical analysis showed no difference between the periods ($p=1.000$).

The average length of hospital stay for patients in period I was 6.98 ± 6.18 (median 5) days which was longer compared to the average length of hospital stay for patients in period II, which was 4.12 ± 4.03 (median 3) days. The analysis revealed a significant statistical difference in the hospitalization time for patients with complicated appendicitis between period I and period II ($p<0.001$).

In period I, an extended hospital stay of more than 5 days occurred in 24 patients (53.3%) operated in 1999, 31 patients (56.4%) operated in 2000, 38 patients (55.1%) operated in 2001, 24 patients (46.2%) operated in 2002, and 12 patients (28.6%) operated in 2003. In period II, an extended stay of more than 5 days occurred in 5 patients (13.5%) operated in 2014, 9 patients (17.6%) operated in 2015, 5 patients (10.6%) operated in 2016, 8 patients (15.7%) operated in 2017, and 4 patients (10.0%) operated in 2018. The analysis showed a statistically significant difference in the extended stay of more than 5 days between the two periods ($p<0.001$).

In each year included in period I, a higher percentage of patients, 49% (129), were hospitalized for more than 5 days compared to each year included in period II, where the figure was equal to 31 patients (13.7%). The analysis showed a significant statistical difference in the hospitalization time of patients with complicated appendicitis for more than 5 days between period I and period II ($p<0.001$).

In the conducted study, it was found that in both period I and period II, the hospitalization time significantly increased with age (period I: $r=0.34$, period II: $r=0.19$), the time elapsed from the onset of symptoms to hospital admission (pre-hospital delay) (period I: $r=0.23$, period II: $r=0.27$), the time from hospital admission to surgery (hospital delay) (period I: $r=0.2$, period II: $r=0.2$), and the duration of the surgery (period I: $r=0.43$, period II: $r=0.33$). Regarding the duration of surgery, statistically significant relationships were found only in period I - the duration of surgery significantly increased with age ($r=0.18$), pre-hospital delay ($r=0.23$), and time from admission to surgery ($r=0.12$). However, in period II, surgery duration did not show any correlation with these factors. Additionally, no relationship between age and pre-hospital delay or hospital delay was found in either period.

In period I, there were 3 (1.1%) deaths among operated patients with complicated appendicitis. In 2000, one patient's death (1.8%) occurred due to complicated appendicitis. In 2001, 2 deaths (2.9%) were recorded. There were no deaths among operated patients with complicated appendicitis in period II.

In period I, a significant association was found between the degree of appendiceal inflammation and the total time of preoperative delays ($p=0.001$). Gangrenous appendicitis occurred significantly more often in patients with delays shorter than 24 hours (79.8%) compared to patients with longer delays (57.1%) ($p<0.05$). Similarly, complicated appendicitis with abscess was significantly more prevalent in patients with delays longer than 24 hours (13.7%) compared to patients with shorter delays (1.1%) ($p<0.05$). Gangrenous appendicitis with perforation occurred more frequently in patients with symptoms lasting more than 24 hours (23.4%) compared to those with symptoms lasting less than 24 hours (16.9%). Likewise, there was a trend that appendicitis with diffuse peritonitis occurred more frequently in patients with symptoms lasting more than 24 hours (5.7%) compared to those with symptoms lasting less than 24 hours (2.2%). However, no significant statistical difference was found. Similar associations were not found in period II ($p=0.208$). However, a trend was observed by which complicated appendicitis and abscess occurred more frequently in patients with symptoms lasting more than 24 hours (18.0%) compared to those with symptoms lasting less than 24 hours (6.3%). No statistically significant difference was found.

A logistic regression model assessed the risk factors for complicated appendicitis. In period I, the model including individual clinical symptoms showed that the risk of developing complicated appendicitis was nearly twice as high in the presence of the Blumberg sign ($OR=2.1$; $p<0.001$) and almost three times as high with leukocytosis above $10,000/\mu\text{l}$ ($OR=2.8$; $p<0.001$) as well as with neutrophils above 75% ($OR=3.0$; $p=0.01$). Complicated appendicitis also occurred more frequently in older individuals, with a risk increase of 2.6% per year of life ($OR=1.03$; $p<0.001$) and in males ($OR=1.5$; $p=0.018$).

In period II, the presence of tenderness in right iliac fossa (odds ratio - $OR = 2.0$; $p < 0.001$), elevated temperature ($OR = 2.0$; $p = 0.012$), and leukocytosis above $10,000/\mu\text{l}$ ($OR = 2.0$; $p = 0.004$) were identified as risk factors. Older age was also a statistically significant factor ($OR = 1.04$; $p < 0.001$), where each additional year of life was associated with a 4.3% increase in risk.

In a situation where multiple symptoms showed a statistical association with the occurrence of appendicitis, a similar relationship was observed in regards to the Alvarado scale. An increase of 1 point in this scale was associated with a 36.1% increase in risk in period I (OR = 1.4; $p < 0.001$) and a 26.8% increase in period II (OR = 1.3; $p < 0.001$). In both periods, the effect of older age was also demonstrated (in period I: OR = 1.02; $p < 0.001$, in period II: OR = 1.04; $p < 0.001$). Only in period I, a statistically significant effect of male gender was observed where the risk of appendicitis was 48% higher in males than in females (OR = 1.5; $p = 0.017$).

Surgical treatment of complicated appendicitis is associated with the occurrence of early postoperative complications. In period I (when only the classical method was used for surgical treatment), the percentage of patients with early postoperative complications was 18.3%, while in period II (with laparoscopic method as the dominant treatment), the percentage of patients with early postoperative complications was only 4.9%. This difference was statistically significant ($p < 0.001$).

In both periods I and II, statistically significant relationships were found between the advancement of appendicitis and the occurrence of early postoperative complications. In period I, the occurrence of early postoperative complications was significantly lower in gangrenous appendicitis (11.7%) compared to gangrenous appendicitis with perforation (37.0%) and complicated appendicitis with abscess formation (29.2%). In period II, the occurrence of early postoperative complications was significantly lower in patients with gangrenous appendicitis (1.7%) compared to those with complicated appendicitis with abscess formation (17.1%) and complicated appendicitis with diffuse peritonitis (15.0%). The occurrence of early postoperative complications in these two types of complicated appendicitis with abscess formation and diffuse peritonitis was also significantly higher than in gangrenous appendicitis (0.0%).

In period I, 11.4% of patients experienced surgical site infection, while in period II, 2.2% of patients had surgical site infection. This difference was statistically significant ($p < 0.001$). All patients with surgical site infection in period I were operated using the classical method, whereas among the 5 patients with surgical site infection in period II, 2 were operated using the classical method and 3 were operated using the laparoscopic method. In period I, the average length of hospital stay for the 30 patients who experienced surgical site infection was significantly longer at 14.0 ± 12.1 (median 10) days, compared to the hospital stay for 233

patients without this complication, which was 6.1 ± 4.2 (median 5) days. Similarly, in period II, a longer length of stay was observed for 5 patients with surgical site infection at 16.6 ± 10.4 (median 19) days, compared to patients without surgical site infection, for whom the average stay was 3.8 ± 3.3 (median 3) days. The analysis showed a statistically significant difference in the length of hospital stay for patients with surgical site infection between periods I II ($p < 0.001$).

In period I, 7 patients (2.7%) developed post-operative intraabdominal abscess, while in period II, this was found in 8 patients (5.5%). In period I, all patients were operated using the classical method. In period II, among the patients who experienced post-operative intraabdominal abscess, 4 (57.1%) were operated using the classical method and 4 (1.8%) were operated using the laparoscopic method. This difference was statistically significant ($p < 0.001$). In period I, the average length of hospital stay for 7 patients who developed intra-abdominal abscess was significantly longer at 24.1 ± 20.5 (median 14) days, compared to the hospital stay for 256 patients without this complication which was equal to 6.5 ± 4.6 (median 5) days. Similarly, in period II, a significantly longer length of stay was observed for 8 patients with intra-abdominal abscess at 16.4 ± 12.6 (median 12) days, compared to patients without it, whose average stay lasted 3.7 ± 2.4 (median 3) days. The analysis showed a statistically significant difference in the length of hospital stay for patients with post-appendectomy intra-abdominal abscess between period I and period II ($p < 0.001$).

In period I, 27 patients (10.3%) experienced early postoperative gastrointestinal obstruction, while in period II there was a statistically significant decrease ($p < 0.001$) with only 5 patients (2.2%) developing it. In period I, all patients underwent classical surgery. In period II, early postoperative gastrointestinal obstruction occurred in 2 patients (28.6%) who underwent classical surgery, while only 3 patients (1.4%) who underwent laparoscopic surgery experienced early postoperative gastrointestinal obstruction. The analysis revealed a significant statistical difference ($p = 0.008$). In period I, the average length of hospital stay for 27 patients with early obstruction was significantly longer at 15.8 ± 8.3 (median 13) days, compared to the hospital stay of 236 patients without this complication, which was 6.0 ± 5.0 (median 5) days. Similarly, in period II, a longer hospital stay of 24.8 ± 13.7 (median 20) days was observed for 5 patients with gastrointestinal obstruction, compared to 3.7 ± 1.8 (median 3) days for patients without the obstruction. The conducted analysis showed a significant statistical difference in the length of hospitalization for patients with early postoperative gastrointestinal obstruction in periods I and II ($p < 0.001$).

In period I, 2 (0.8%) patients were found to experience postoperative bleeding, while in period II, only 1 (0.4%) patient was observed with postoperative bleeding. In period I, both patients underwent classical surgery while in period II, the one patient underwent laparoscopic surgery.

In the conducted study, only 1 case of intestinal/fecal fistula was observed in period I.

In period I, the study evaluating the risk of prolonged hospital stay exceeding 5, a higher risk was associated with age (OR=1.05; $p<0.001$) as well as gender, with men having the risk nearly twice as high (OR=1.9; $p=0.027$). Furthermore, the risk increased over 4-fold in patients with neutrophilia above 75% (OR=4.3; $p=0.011$) and nearly 2-fold in patients with elevated body temperature (OR=1.9; $p=0.032$). Elevated body temperature was also a risk factor for prolonged hospitalization in period II, where an almost 4-fold increase in risk was observed (OR=3.7; $p=0.009$). A statistically significant relationship was also found for the Blumberg sign as its presence was associated with a more than 5-fold decrease in the risk of prolonged hospital stay (OR=0.19; $p=0.01$).

In the second model which included the Alvarado scale, only age (OR=1.05; $p<0.001$) and male gender (OR=1.9; $p=0.027$) were confirmed to have a significant correlation with prolonged stay in period I, at a very similar level to the previous model.

The risk factors for prolonged hospital stay in period I were age (OR=1.06; $p<0.001$), as well as pre-hospital delay and duration of the surgery. The time from diagnosis to admission to the ward was associated with a 1.6% increase in risk per hour (OR=1.02; $p=0.002$), and the duration of the procedure with a 2.8% increase in risk per minute (OR=1.028; $p<0.001$). In period II, the risk of prolonged stay was significantly associated with gender, being almost 60% lower in men (OR=0.41; $p=0.042$). Moreover, the risk of prolonged stay increased with increasing hospital delay by 4% per hour (OR=1.04; $p=0.03$), and with the prolonged duration of the surgery by 1.9% per minute (OR=1.02; $p=0.012$).

CONCLUSIONS

1. Unusual positioning of the appendix is risk factor for the development of complicated appendicitis that we have no influence over.
2. The time that elapses from the onset of symptoms of acute appendicitis to the hospital admission should be shortened.

3. The time that elapses from hospital admission to surgical intervention should be shortened and is a risk factor for the occurrence of complicated appendicitis and postoperative complications that we have influence over, and it should be minimized as much as possible.

4. Laparoscopic surgery is a safe and effective method for the surgical treatment of complicated appendicitis and it significantly reduces treatment costs.

5. The increasing average age of the population may result in a higher number of elderly patients with complicated appendicitis.

STATISTICAL METHODS

In the statistical analysis evaluating relationships between qualitative and ordinal variables, Fisher's Exact Tests were for 2x2 tables and, in the case of larger tables, Fisher-Freeman-Halton tests were applied. When more than 2 qualitative categories were compared, additional tests for two proportions were employed, applying Bonferroni correction for multiple comparisons as post hoc tests. In order to assess the incidence of changes in proceeding time periods as well as for time-related categorical variables, χ^2 tests were employed for linear trends, explicitly indicating their usage in each case. In the case of quantitative variables, inter-group comparisons were conducted using the non-parametric Mann-Whitney U test. Correlations between variables of continuous or ordinal nature were measured using the non-parametric Spearman Rank Correlation Coefficient. Multivariable logistic regression models were utilized to assess risk factors for dichotomous features. Statistical hypotheses were tested at the 95% significance level. Calculations were conducted using the 26.0 version of the IBM SPSS Statistics software. IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.