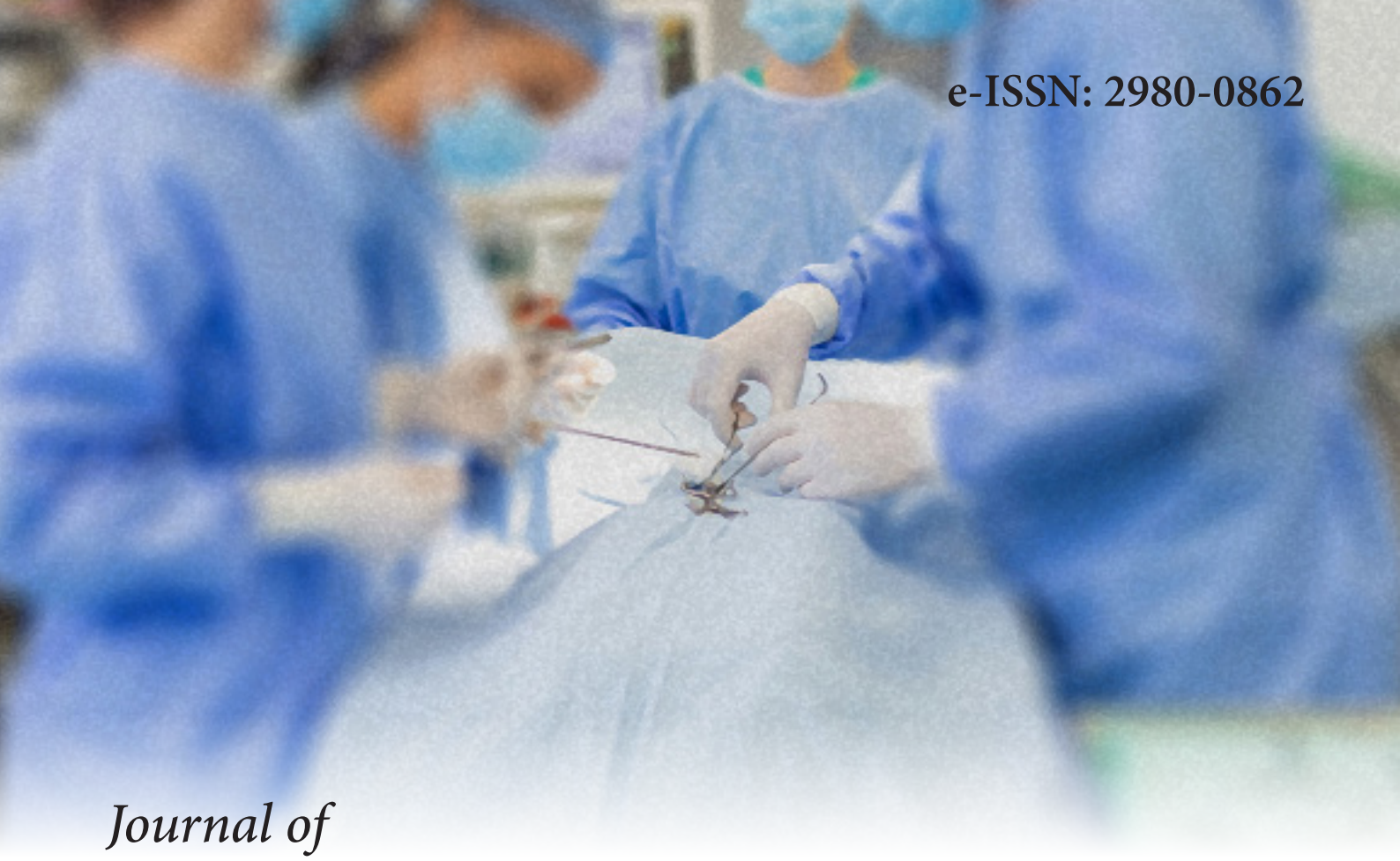

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Rate and risk factors of surgical site infection following abdominal surgery; a prospective study

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ABSTRACT

Aims: Surgical site infection (SSI) remains a significant cause of morbidity and financial burden on patients. This study aimed to describe the incidence and risk factors associated with developing SSI in adult patients after abdominal surgery.

Methods: In this 6-month prospective observational study, adult patients undergoing abdominal surgery at the gastrointestinal surgery unit of our tertiary referral center were included. Excluded from the study were patients lost to follow-up; additionally, this study does not include urological, gynecological, vascular, plastic, or transplant surgeries. Patients were followed up for 30 days, data collection was done using a standardized data collection form, and SSI was diagnosed according to the Centers for Disease Control and Prevention definition. Univariate and multivariate analyses were performed to identify risk factors for SSI.

Results: The study included a total of 212 patients. The incidence of SSI was 32.5%. Emergency operations, male gender, and high body-mass index were identified as independent predictors of SSI. The most commonly isolated organisms in analyzed cultures were *Klebsiella* spp.

Conclusion: A high rate of SSI following abdominal surgery was observed. Periodic audits to assess compliance with established standard infection control measures, review of prophylactic antibiotic guidelines, as well as addressing modifiable risk factors have the prospect of reducing SSI.

Keywords: Surgical site infection, abdominal surgery, risk factors, antibiotic resistance

INTRODUCTION

Surgical site infection (SSI) is a common complication following surgery and one of the most common preventable healthcare-associated infections. SSI occurs in 0.6% to 9.5% of all surgical procedures, according to the type of surgery.[1] According to a multicenter 18-month prospective study in 2016, the incidence of SSI in Egypt is 12%.[2] Incidences as high as 15%-25% have been reported following abdominal surgeries and up to 39.8% following gastrointestinal surgeries depending on the contamination level of the surgical wound.[3,4]

According to the Center for Disease Control and Prevention's National Health Safety Network (CDC/PNHSN) of the United States, an infection in the area where surgery took place, occurring within 30 days after surgery (or up to 1 year when an implant is utilized) is considered SSI. This is further classified into superficial incisional (infections involving only the skin and subcutaneous tissue), deep incisional (infections involving muscle and fascial layers), and organ/space SSI (Infection involving any part of the anatomy deep to muscle/fascia layers).[5-7]

Compared to uninfected patients, patients who develop SSI have longer postoperative hospital stay in the wards and intensive care units (ICU), and increased requirements for further interventions including additional medications, investigations, and hospital readmission. An increased need for further surgical interventions ranging from imaging-guided procedures to outright reoperation is also seen in this group of patients. Prolonged hospitalization and the need for further therapy, as a consequence, incur additional costs. All these, in addition to intangible costs of pain and suffering, affect patients' quality of life, increasing postoperative morbidity and risk of mortality in SSI patients.[8,9]

Many factors that put surgical patients at risk of developing SSI have been reported. The CDC's National Nosocomial Infections Surveillance System (NNIS) risk index is a model of SSI risk prediction that has been relatively accurate in abdominal surgeries. The components of the NNIS risk index include the ASA score, surgical wound class, and duration of operation.[10,11] Other recognized risk factors include high body-

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mass index (BMI), advancing patient age, malignancy, diabetes mellitus, previous radiation or chemotherapy, smoking, and preoperative hair removal a day before surgery.[12,13]

The main goal of our study was to describe the incidence and identify the risk factors associated with developing SSI in adult patients undergoing abdominal surgery. The secondary goals were to identify organisms causing SSI and their antibiotic resistance pattern; assess postoperative morbidity using the Clavien-Dindo classification; and the influence of SSI on length of postoperative hospital stay.

METHODS

Ethics

Ethical approval was obtained from the Alexandria University Ethics Committee (Date: 15.12.2022, Decision No: 0107502). Informed consent was obtained from all participants in the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

This six-month prospective observational study was conducted at the Gastrointestinal Surgery Unit of our Tertiary Referral Center and included patients aged ≥18 undergoing abdominal surgery between November 1st, 2022, and April 30, 2023. Patients whose wounds were not primarily closed, as well as those lost to follow up, were excluded. This study does not include abdominal procedures for urological, vascular, plastic, gynecological or transplant surgeries as those procedures are not part of the spectrum carried out at our surgery unit.

Study Technique

All patients were admitted through the outpatient clinic or emergency department. Preoperative assessment included thorough history taking, clinical examination, and investigations. All patients received pre-operative prophylactic antibiotics according to the Alexandria Main University Hospital Surgical prophylaxis guidelines (2 g cefoxitin/ceftriaxone for non-gastrointestinal surgeries; IV 500 mg metronidazole added for gastrointestinal surgeries, pancreatic and emergency hernia surgeries. IV 400 mg ciprofloxacin+metronidazole used for biliary surgeries) at induction of anesthesia. Skin preparation was done with povidone-iodine (Betadine®) before skin incision. Patients were monitored for signs of SSI in the ward and followed up in the outpatient clinic after discharge for 30 days after surgery. SSI was diagnosed according to the CDC/PNHSN definition. Patients who developed SSI had wound discharge taken from infected wounds and sent for culture and sensitivity and findings were recorded.

Data Collection

Data collection was done using a standardized data collection form.

Preoperative data included demographic data, past medical and surgical history, drug/therapy history (steroid, chemotherapy, radiotherapy), and smoking history. BMI (kg/m^2) and ASA Classification, preoperative hemoglobin, blood urea and serum creatinine, and serum albumin.

Intraoperative data included urgency of operation (elective or emergency), the surgeon (consultant or trainee), use of general anesthesia (GA), approach (open or laparoscopic), duration of the procedure, blood transfusion, surgical wound classification and gastrointestinal (GIT) surgery (yes or no); defined as any operation involving transmural breach (repair of perforation, transection, resection, re-anastomosis, creation or reversal of stoma) in any part of the GIT from the lower esophagus to the rectum including extra-hepatic biliary tract.

Postoperative data postoperative length of hospital stay, ICU admission, postoperative morbidity and mortality assessed by Clavien-Dindo classification.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level. An initial comparison of all independent variables between the groups of patients with and without SSI was done. The dependent variable was SSI. Chi-square test (for categorical variables), Fisher's exact or Monte Carlo correction (Correction for Chi-square when more than 20% of the cells have an expected count of less than 5), student t-test (for normally distributed quantitative variables) and Mann-Whitney test (for abnormally distributed quantitative variables) were the tests used. For the variables that showed statistically significant differences (p-value <0.05) between both groups, univariate and multivariate logistic regression analyses were done to identify risk factors for developing SSI.

RESULTS

The study included 212 patients; 117 (55.2%) were male, and 95 (44.8%) were female. The mean age of the study population was 45±16 years. Six patients died before the end of 30 days of follow-up.

Fifty-nine (27.8%) patients were smokers, 35 (16.5%) were diabetic, 35 had cardiovascular (CVS) disease, 32 had malignant diseases, and 25 (11.8%) had a history of previous laparotomy.

One hundred and forty-one (66.5%) patients underwent elective surgery. Sixty-two cases (29.2%) were performed laparoscopically. GIT surgeries made up 65.6% (n=139) of cases. The mean operative time was 136.5 minutes. The majority of the procedures (110, 51.9%) were classified as clean-contaminated, while 62 (29.2%) were classified as either contaminated or dirty procedures.

The overall rate of SSI was 32.5% (69/212). Forty (58%) of the patients with SSI had superficial infections, 24 (34.8%) had deep infections, and 5 (7.2%) had organ/space SSI (**Table 1**). Incidence was 49.2% and 24.1% in emergency and elective surgery, respectively. The rate of SSI following laparoscopic surgeries was 14.5% and 40% following open surgeries. The observed rates of SSI in the different wound classes were recorded (**Table 2**); 12.5% in clean wounds, and 75% dirty wounds. The incidence of SSI in GIT surgeries was 36.7%. **Table 3** shows the incidence per surgical procedure included in this study.

Table 1. Proportion of SSI by depth of tissue involved

Class	No (total SSI=69)	Percentage
Superficial incisional	40	58%
Deep incisional	24	34.8%
Organ/space	5	7.2%

SSI: Surgical site infection

Table 2. Surgical site infection rate according to wound class *p<0.001 highly significant (χ2=24.314)

Wound class	Total (n=212)	SSI (n=69)	Percentage of SSI
Clean	40	5	12.5%
Clean-contaminated	110	30	27.2%
Contaminated	50	25	50%
Dirty	12	9	75%

*: Statistically significant at p≤0.05. χ : Chi square test. SSI: Surgical site infection

Table 3. Surgical site infections according to surgical procedure

Procedure	No of patients (n=212)	No of SSI (n=69)	Percentage (%)
Laparoscopic cholecystectomy	37	5	13.5
Colon and rectal surgery	30	15	50
Incisional hernia repair	16	5	31.3
Other hernia repair	30	5	16.7
Exploratory laparotomy	33	17	51.5
Appendectomy	19	6	31.6
Pancreatic, hepatic, and biliary surgery	21	10	47.6
Gastrectomy, gastrojejunostomy, bariatric	14	3	21.4
Other	12	3	25

SSI: Surgical site infection

Table 4. Comparison of demographic and preoperative data of patients with and without SSI

Variable	Total (n=212) No.‡	Total (n=212) %‡	No SSI (n=143) No.‡	No SSI (n=143) %‡	SSI (n=69) No.‡	SSI (n=69) %‡	Test of sig.	p-value
Gender								
Male	117	55.2	71	49.7	46	66.7	χ^2=5.449	0.020*
Female	95	44.8	72	50.3	23	33.3		
Age (years) mean±SD	45.1±16.0		44.5±16.0		46.2±16.2		t=0.716	0.475
Diabetic	35	16.5	19	13.3	16	23.2	χ^2=3.311	0.069
Cardiovascular disease	35	16.5	24	16.8	11	15.9	χ^2=0.024	0.877
Cancer	32	15.1	17	11.9	15	21.7	χ^2=3.524	0.060
Liver disease	11	5.2	4	2.8	7	10.1	χ^2=5.108	FEp=0.042*
Previous laparotomy	25	11.8	12	8.4	13	18.8	χ^2=4.885	0.027*
Smoking	59	27.8	37	25.9	22	31.9	χ^2=0.837	0.360
Steroid	2	0.9	1	0.7	1	1.4	χ^2=0.280	FEp=0.546
Chemotherapy	9	4.2	4	2.8	5	7.2	χ^2=2.266	FEp=0.155
ASA class								
I	71	33.5	63	44.1	8	11.6		
II	74	34.9	50	35.0	24	34.8	χ^2=30.624	<0.001*
III	38	17.9	16	11.2	22	31.9		
IV	29	13.7	14	9.8	15	21.7		
≠HBsAg								
Negative	156	73.6	108	75.5	48	69.6	χ^2=1.407	MCp=0.546
Positive	4	1.9	2	1.4	2	2.9		
≠HCV-Ab								
Negative	154	72.6	109	76.2	45	65.2	χ^2=7.483	MCp=0.021*
Positive	6	2.8	1	0.7	5	7.2		
BMI (kg/m²) median (IQR)	28.0 (24.4-31.0)		28.0 (23.8-30.0)		29.0 (28.0-32.0)		U=3251.0	<0.001*
Pre-op stay (days) median (IQR)	5.0 (1.0-12.0)		6.0 (2.0-12.0)		2.0 (1.0-9.0)		U=3816.50	0.008*
Hemoglobin (g/dl) mean±SD	12.8±2.4		12.9±3.2		12.8±1.9		t=0.202	0.840
≠Albumin (g/dl) median (IQR)	4.2 (3.7-4.5)		4.30 (4.0-4.6)		4.0 (3.40-4.30)		U=1456.5	<0.001*
Urea (mg/dl) median (IQR)	28.0 (24.0-39.0)		28.0 (24.0-36.0)		28.0 (24.0-43.0)		U=4697.0	0.571
Creatinine (mg/dl) median (IQR)	0.8 (0.6-0.9)		0.70 (0.6-0.9)		0.80 (0.6-1.0)		U=4096.0	0.043*

SSI: Surgical site infection, SD: Standard deviation, ASA: American Society of Anesthesiologists, HBsAg: Hepatitis B surface antigen, HCV-Ab: Hepatitis C virus antibody, BMI: Body-mass index, IQR: Interquartile range, c^2: Chi-square test, FE: Fisher exact, U: Mann-Whitney test, t: Student t-test, *: Statistically significant at p≤0.05, ≠: n<212, ‡: unless specified

In the initial comparison of risk variables between patient groups with and without SSI, diabetes mellitus, smoking, use of GA, and 30-day postoperative mortality showed no statistically significant difference between the two groups. (Table 4, 5).

Multivariate analyses identified emergency operations [OR=4.640, 95% confidence interval (CI)=1.061-20.282], male gender (OR=2.678, 95% CI=1.152-6.222), and higher BMI (OR=1.133, 95% CI=1.059-1.21) as independent predictors of SSI.

Other risk factors associated with SSI identified from univariate analyses included lower serum albumin, ASA class of >II, previous laparotomy, intraoperative blood transfusion, contaminated/dirty wound class, longer duration of operation, postoperative ICU admission, >class II of the Clavien-Dindo classification of postoperative morbidity, and longer postoperative hospital stay (Table 6). Serum albumin and HCV-Ab were excluded from multivariate analysis as they were not tested in all patients.

From a total of 65 samples collected, we obtained 74 isolates. Gram-negative bacilli accounted for 82% (n=61) of the cultured organisms and 95% of those organisms exhibited the following pattern of antibiotic resistance: multi drug resistant (MDR) (resistant to ≥1 agent in ≥ 3 antimicrobial categories)=31.1% (19/61); extended drug resistant (XDR) (resistant to ≥ 1 agent in all but 2 or fewer antimicrobial categories)=60.7%; Pan drug resistant (PDR) (resistant to all agents in all antimicrobial categories)=3.3% (Table 7). The majority of the samples cultured a single organism and the most commonly isolated organism was *Klebsiella* spp. (34 isolates, 45.9%) followed by *E. coli* (12 isolates, 16.2%) and *Acinetobacter baumannii* (9 isolates, 12.1%). Six cultures (8.1%) yielded no growth (Figure).

DISCUSSION

The overall incidence of SSI in our study was 32.5%. Our rate is higher than many other reported incidences in other lower-middle-income countries in Africa and Asia, ranging from 13-30.7%.[14-18] Interestingly, Deyem et al.[19] findings in Congo are similar to ours at 32.6%. In another study in Egypt by Ghanem et al.[20] a rate of 38.6% was observed. The high incidence observed in our study can partly be attributed to hospital environment-related factors, the complexity of procedures, and the absence of an instituted active surveillance system. In addition, this study was conducted in a low- to mid-income country with surgical resource constraints. Our

Table 5. Comparison of operative and postoperative data of patients with and without SSI

Variable	Total (n=212) No.‡	%‡	No SSI (n=143) No.‡	%‡	SSI (n=69) No.‡	%‡	Test of sig.	p-value
Surgeon								
Consultant	71	33.5	49	34.3	22	31.9	χ^2=0.119	0.731
Trainee	141	66.5	94	65.7	47	68.1		
Operative type								
Elective	141	66.5	107	74.8	34	49.3	χ^2=13.640	FEp<0.001*
Emergency	71	33.5	36	25.2	35	50.7		
Approach								
Open	150	70.8	90	62.9	60	87.0	χ^2=12.977	<0.001*
Laparoscopic	62	29.2	53	37.1	9	13.0		
Gastrointestinal surgery								
Yes	139	65.6	88	61.5	51	73.9	χ^2=3.157	0.076
No	73	34.4	55	38.5	18	26.1		
General anesthesia	189	89.2	124	86.7	65	94.2	χ^2=2.699	0.100
Surgical wound class								
Class I	40	18.9	35	24.5	5	7.2		
Class II	110	51.9	81	56.6	30	43.5	χ^2=24.314	<0.001*
Class III	50	23.6	25	17.5	25	36.2		
Class IV	12	5.7	3	2.1	9	13.0		
Blood transfusion	51	24.1	25	17.5	26	37.7	χ^2=10.394	0.001*
Drain	182	85.8	118	82.5	64	92.8	χ^2=4.014	0.045*
Duration of surgery (min.), median (IQR)	136.5 (104-200)		130.0 (99-192)		183.0 (130-215)		U=3196.500	<0.001*
Skin closure								
Suture	170	80.6	118	83.1	52	75.4	χ^2=1.775	0.183
Staple	41	19.4	24	16.9	17	24.6		
Intensive care unit admission	47	22.2	23	16.1	24	34.8	χ^2=9.431	0.002*
Mortality	6	2.8	2	1.4	4	5.8	χ^2=3.274	FEp=0.089
Clavien Dindo class								
≤II	165	77.8	121	84.6	44	63.8	χ^2=11.723	0.001*
III-V	47	22.2	22	15.4	25	36.2		
Post-operative stay (d), median (IQR)	4.0 (2.0-6.0)		3.0 (1.0-5.50)		6.0 (4.0-10.0)		U=2661.50	<0.001*

SSI: Surgical site infection, Min: Minute, IQR: Inter quartile range, c^2: Chi-square test, FE: Fisher exact, U: Mann Whitney test, ‡: unless specified, *: Statistically significant at p≤0.05

Table 7. Pattern of antibiotic resistance among gram-negative isolates

	Total isolates	MDR No. (%)	XDR No. (%)	PDR No. (%)
Klebsiella spp.	34	6 (17.6)	26 (76.5)	2 (5.9)
Escherichia coli	12	6 (50.0)	4 (33.3)	0 (0.0)
Acinetobacter baumannii	9	3 (33.3)	6 (66.7)	0 (0.0)
Proteus mirabilis	3	2 (66.7)	1 (33.3)	0 (0.0)
Pseudomonas aeruginosa	3	2 (66.7)	0 (0.0)	0 (0.0)
Total	61	19 (31.1)	37 (60.7)	2 (3.3)

MDR: Multi drug resistant (resistant to ≥1 agent in ≥3 antimicrobial categories), XDR: Extended drug resistant (resistant to ≥1 agent in all but 2 or fewer antimicrobial categories), PDR: Pan drug resistant (resistant to all agents in all antimicrobial categories)

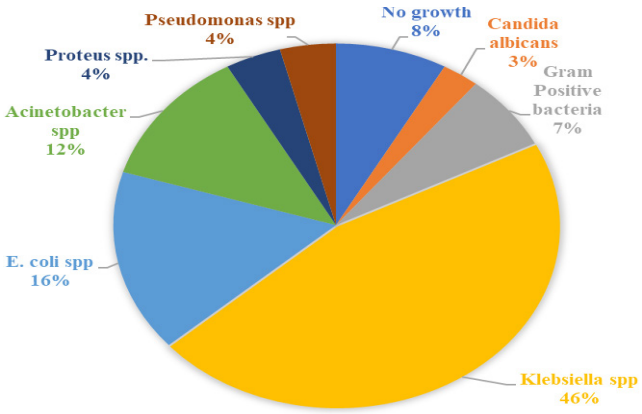

Figure. Culture report

findings highlight insufficient awareness of hospital-acquired infections alongside subpar infection control measures in our center.

The authors also observed that, consistent with existing literature, the incidence of SSI rose progressively from clean to dirty wounds.[3,15,21]

The independent risk factors identified in the multivariate analysis in our study were male gender, emergency surgery, and high BMI (>28 kg/m^2). Male patients were almost three

Table 6. Univariate and multivariate logistic regression analyses to detect the most independent risk factors

Variable	Univariate p-value	Univariate OR (LL-UL 95% CI)	Multivariate p-value	Multivariate OR (LL-UL 95% CI)
Male gender	0.021*	2.028 (1.115 - 3.689)	0.022*	2.678 (1.152-6.222)
Liver disease	0.034*	3.923 (1.108-13.893)	0.134	4.628 (0.623-34.366)
Previous laparotomy	0.031*	2.534 (1.089-5.898)	0.335	1.748 (0.561-5.443)
≠Albumin (mg/dl)	<0.001*	0.267 (0.138-0.519)		
Creatinine	0.018*	1.937 (1.119 - 3.355)	0.465	1.110 (0.838-1.471)
≠HCV-Ab positive	0.025*	12.111 (1.376 - 106.598)		
Body-mass index (kg/m^2)	0.003*	1.078 (1.027 - 1.132)	<0.001*	1.133 (1.059-1.213)
ASA score (III & IV) vs (I & II)	<0.001*	4.355 (2.340 - 8.106)	0.466	1.419 (0.554-3.6631)
Pre-operative stay (days)	0.302	0.976 (0.932-1.022)		
Urgency of operation (emergency)	<0.001*	3.060 (1.672 - 5.600)	0.041*	4.640 (1.061-20.282)
Approach (open)	0.001*	3.926 (1.802 - 8.551)	0.155	2.568 (0.701-9.404)
Blood transfusion	0.002*	2.854 (1.489 - 5.470)	0.908	0.940 (0.331-2.672)
Drain	0.052	2.712 (0.990 - 7.425)		
Duration of surgery (min.)	<0.001*	1.007 (1.003-1.011)	0.486	1.002 (0.996-1.008)
Surgical wound class (III & IV vs I & II)	<0.001*	3.990 (2.131 - 7.470)	0.117	2.120 (0.828-5.425)
Intensive care unit admission	0.003*	2.783 (1.429 - 5.420)	0.683	0.781 (0.238-2.559)
Clavien Dindo (≥III)	0.001*	3.125 (1.601-6.100)	0.809	1.169 (0.329-4.146)
Post-operative stay (days)	<0.001*	1.263 (1.155-1.381)	0.059	1.141 (0.995-1.307)

OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper limit, HCV-Ab: Hepatitis C virus antibody, ASA: American Society of Anesthesiologists, Min: Minute, *: Statistically significant at p≤0.05, ≠: Excluded from multivariate because n<212

times more likely to develop SSI compared to females. Similar findings have been reported in the literature.[3,14,22] The specific reason for male susceptibility was not evaluated in this study. The odds of developing SSI following emergency surgery were 4.6 times higher than those of elective surgery. This compares favorably with similar studies that identify emergency operation as an independent risk factor in multivariate analyses.[3,23] Patients with higher BMI were at an increased risk of developing SSI, a trend consistently supported by existing medical research.[24-26]

Univariate logistic regression analysis identified some other known risk factors assessed in our study that might have played a role in the high incidence observed in our study. Factors correlated with higher risk of SSI in univariable analysis were: history of previous laparotomy, lower serum albumin (mean of 3.8 vs 4.2 in SSI Vs no SSI, p<0.001), higher serum creatinine, ASA class of more than II, intraoperative blood transfusion, contaminated/dirty wound class, duration of operation >130 minutes, and postoperative ICU admission. The median postoperative length of the hospital stay was also longer in patients with SSI compared to patients without SSI (6d vs 3d, p<0.001). These observations are akin to previously reported findings in the literature.[26-31] The odds of developing SSI in patients with liver disease were 3.9, and patients who tested positive for HCV Ab also had a significantly higher risk. The association of liver disease and hepatitis C-positive status with SSI is not novel.[32-34]

The patients' age and presence of cardiovascular disease were not risk factors for developing SSI in our study. A similar outcome has been reported previously in the literature.[23] Although these findings are contrary to those previously reported in Alexandria, Egypt.[35] Smoking status was not a predictor of SSI in our study and compares favorably with a large study (n=1.062) assessing risk factors of SSI.[36]

The proportion of diabetic patients was higher in the SSI group (16/69; 23.2%) than those without SSI (19/143; 13.3%), the difference was, however, not statistically significant (p-value=0.069). This compares favorably with findings reported by Hafez et al.[36] in Egypt and compatible with findings elsewhere by Ott et al.,[37] Adejumo et al.,[38] Cheuk et al.[39] and Watanabe et al.[23] The authors observed that this index study and the above-listed studies that reported similar findings about diabetes and SSI identified other factors like high BMI, contaminated wound, and prolonged procedural time on logistic regression analysis. Suggesting that these other factors are the true drivers of SSI, eliminating diabetes as an independent risk variable, contrary to common findings in established literature. The presence of malignant disease did not increase the risk of SSI in our study.

The use of GA and placement of drains were not identified as risk factors for SSI in our study, and a similar outcome has been reported.[35] No difference was demonstrated in the rate of SSI in surgeries performed by consultants versus trainees, probably because consultants performed more complex procedures with longer procedural time, which increased the odds of SSI in our univariate analysis.

The rate of mortality was higher in the patient with SSI compared to those without SSI (5.8% vs 1.4%) but it was not statistically significant (p=0.089).

Gram-negative bacilli were the most commonly isolated organisms. The most implicated organism was *Klebsiella* spp. (45.9%) followed by *E. coli* (16.2%). Similar findings were reported by Abduo et al.[2] and Baro et al.[14] In a similar study by Alkaaki et al.,[3] *E. coli* (52%) was the predominant isolate followed by gram-positive bacteria (38%). Some studies have, however, revealed a predominance of gram-positive bacteria like *Staphylococcus aureus,* and *Enterococcus.*[40,41] Ninety-five percent of the cultured gram-negative bacilli in our study exhibited MDR/XDR/PDR. MDR organisms resist standard prophylactic antibiotics, they lead to higher rates of wound complications like SSIs. Consequently, these infections are associated with prolonged hospital stays and expensive specialized therapies.[42,43] We also found that only 19% of cultured organisms were sensitive to the prophylactic antibiotics used. These findings challenge the appropriateness of the current antibiotic prophylaxis protocol of our institution and call for urgent revision of the current guidelines.

Limitations

This is a single-center study that reflects a specific culture, population, and care protocol that may differ from practices elsewhere. While the standard surveillance time for SSI is 30 days as applied in our study, the optimal follow-up time for implant-based surgeries like hernioplasty is 90 days to a year, hence, the 30-days follow up represents another limitation of this study. The use of logistic regression analysis was to control for confounding factors to improve the validity of this observational study, however, some variables like the serum albumin level, were not analyzed in the multivariate regression model, as it was not done for all patients. The authors also wish to point out that the case-mix heterogeneity ranging from clean to contaminated/dirty procedures in the index study might skew and inflate the overall incidence of SSI.

CONCLUSION

A high rate (32.5%) of SSI following abdominal surgery was detected in our study. Fifty-eight percent of SSI cases were superficial incisional infections with no serious consequences. Male gender, emergency surgery, and high BMI were identified as independent risk factors for developing SSI following abdominal surgery. A number of other factors increasing susceptibility to SSI were also identified in the univariate analyses, including the components of NNIS risk index. M/XDR gram-negative bacilli were the most common isolates in the analyzed cultures. The most commonly isolated organism was *Klebsiella* spp. Ensuring the implementation of well-structured policies of infection control by periodic auditing; review of prophylactic antibiotic guidelines, as well as addressing modifiable risk factors have the prospect of reducing SSI.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Alexandria University Ethics Committee (Date: 15.12.2022, Decision No: 0107502).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All

participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: MRE; Design: HIA; Control: MM; Resources: AAG, MRE; Materials: AAG; Data Collection and/or Processing: HIA, MM; Analysis and/or Interpretation: MM; Literature Review: HIA; Writing the Article: HIA; Critical Review: MRE, AAG.

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What do the numbers say and what do surgeons choose? A national analysis of general surgery subspecialty placements in Turkiye

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ABSTRACT

Aims: General surgery subspecialty training is influenced not only by individual career preferences but also by institutional capacity, regional inequalities, and changing professional expectations. Despite increasing quotas in recent years, declining occupancy rates suggest that subspecialty preferences may reflect broader professional and structural factors. This study aimed to evaluate temporal trends, occupancy rates, and regional/institutional distribution patterns of general surgery subspecialty placements in Turkiye.

Methods: Placement data from general surgery subspecialty programs between 2015 and 2025 were retrospectively analyzed. Examination year, placement type, subspecialty branch, hospital category, geographic region, quotas, vacant positions, and occupancy rates were evaluated using descriptive statistics.

Results: A total of 503 placement records comprising 757 quotas were analyzed, of which 68.4% were filled. Occupancy rates declined from 82.8% in 2015-2019 to 58.0% in 2020-2025 despite increasing quotas. Surgical oncology (80.6%) and gastrointestinal surgery (75.5%) had the highest occupancy rates, whereas intensive care (45.8%) and hand surgery (34.8%) showed substantially lower occupancy. Most quotas were concentrated in university hospitals and metropolitan cities. Additional placement quotas demonstrated markedly lower occupancy rates (34.9%) and accounted for a considerable proportion of vacant positions.

Conclusion: Although general surgery subspecialty training in Turkiye has expanded quantitatively over the last decade, occupancy rates have declined significantly, particularly after 2020. These findings suggest that subspecialty preferences are shaped not only by numerical quota increases but also by factors such as workload, training environment, burnout, career sustainability, and quality of life. A more comprehensive workforce planning strategy considering surgeons' professional expectations may therefore be necessary.

Keywords: Workforce planning, surgical workforce, fellowship selection, regional disparities, career sustainability, physician burnout

INTRODUCTION

Subspecialty training in general surgery represents one of the most critical stages in the development of the surgical workforce, shaping not only individual career trajectories but also the long-term sustainability and organizational structure of healthcare systems. In many countries, increasing subspecialization has become an inevitable consequence of technological advancement, expanding multidisciplinary care, growing oncological complexity, and rising expectations regarding surgical outcomes and expertise. However, the expansion of subspecialty training opportunities does not necessarily translate into proportional trainee demand, and the relationship between workforce planning and physician preferences has become increasingly complex over the last decade.[1,2]

In Turkiye, the Subspecialty Education Examination (YDUS) constitutes the primary mechanism for placement into general surgery subspecialty programs, including surgical oncology, gastrointestinal surgery, critical care, and hand surgery. Although the number of training positions has increased considerably in recent years, concerns regarding vacant quotas, uneven institutional distribution, and declining occupancy rates have become more prominent. These changes appear to reflect not only numerical imbalances between supply and demand but also broader transformations in the professional expectations of surgeons. Contemporary surgical career decisions are increasingly influenced by factors such as workload intensity, burnout, work-life balance, medicolegal pressure, academic opportunities, institutional support, and

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long-term career sustainability. Consequently, subspecialty preference patterns may provide indirect yet valuable insight into the evolving professional dynamics of the surgical workforce.

Recent literature has emphasized that burnout and dissatisfaction among surgeons and surgical trainees are becoming globally significant concerns. Systematic reviews have demonstrated strong associations between burnout, excessive workload, emotional exhaustion, impaired work-life balance, and declining professional satisfaction among surgeons and trainees.[1,2] In parallel, studies conducted in Turkiye have similarly highlighted substantial levels of burnout among general surgeons and have underscored the impact of working conditions and educational environments on professional well-being.[3] Furthermore, national surveys evaluating surgical residency training have demonstrated persistent concerns regarding educational quality, mentorship, operative exposure, and institutional support.[4] Collectively, these findings suggest that modern surgical career preferences are increasingly shaped by lifestyle considerations and training conditions in addition to academic interest alone.

The present study is particularly important because the decline in quota occupancy observed after 2020 coincided with a marked increase in the total number of opened positions. As demonstrated in the current dataset, overall fill rates declined from 82.8% during 2015-2019 to 58.0% during 2020-2025 despite substantial quota expansion. Moreover, this decline was not homogenous across subspecialties; while surgical oncology and gastrointestinal surgery maintained relatively high occupancy, critical care and hand surgery experienced pronounced decreases in fill rates. The distribution of quotas was also heavily concentrated within metropolitan cities and university hospitals, suggesting substantial institutional and geographic centralization in subspecialty training.

Despite ongoing discussions regarding surgical workforce planning and subspecialty training in Turkiye, the existing literature remains limited to institutional experiences, surveys, or specialty-specific observations. To our knowledge, no previous national-scale study has comprehensively evaluated general surgery subspecialty placements over an extended period while simultaneously examining temporal trends, institutional concentration, regional distribution, and quota occupancy dynamics. Therefore, the present study aimed to analyze general surgery subspecialty placement data in Turkiye between 2015 and 2025 in order to characterize temporal changes in quota distribution and occupancy patterns and to evaluate the structural transformation of subspecialty training from both workforce and professional perspectives.

We anticipated that the substantial increase in subspecialty training quotas after 2020 would not be accompanied by proportional increases in occupancy rates and that occupancy patterns would vary according to subspecialty branch and institutional characteristics.

METHODS

Ethics

Since this study was conducted exclusively using publicly accessible, anonymized, and non-identifiable administrative data obtained from the official ÖSYM database, formal ethics committee approval and informed consent were waived in accordance with national regulations and the principles of the Declaration of Helsinki. No patient-level or personally identifiable information was accessed, and all data were evaluated in an anonymous manner.[8]

This retrospective, descriptive, nationwide study analyzed placement data from the Turkish Medical Subspecialty Examination (YDUS) for general surgery subspecialties between 2015 and 2025. Publicly accessible placement records published by the Measurement, Selection and Placement Center (ÖSYM) were systematically reviewed and analyzed.[5] The study aimed to evaluate temporal changes in quota distribution, occupancy dynamics, institutional concentration, and regional variation in general surgery subspecialty training across Turkiye.

The unit of analysis was defined as each individual placement record corresponding to a specific examination cycle, subspecialty branch, and training institution combination. Variables extracted from the dataset included examination year, examination period (spring or fall), placement type (initial or additional placement), subspecialty category, hospital type, geographic region, metropolitan municipality status, number of opened quotas, number of vacant quotas, and quota fill rates. Subspecialty branches were categorized as surgical oncology, gastrointestinal surgery, critical care, hand surgery, and other subspecialties. Hospital types were classified as university hospitals, training and research hospitals, and city hospitals. Geographic regions were grouped according to the official geographical regions of Turkiye. Metropolitan status was determined according to the legal metropolitan municipality designation.

The primary outcome variable was defined as a "fully filled quota," indicating that all positions opened within a placement record were occupied during the corresponding placement cycle. Aggregate fill rate was calculated using the formula: (number of filled quotas/total opened quotas)×100. Comparisons between study periods were performed using two predefined temporal intervals: 2015-2019 and 2020-2025. This categorization was established to evaluate structural changes in placement dynamics during the post-2020 period, when a substantial expansion in quota numbers became evident.

Statistical Analysis

Descriptive statistics were presented as number and percentage for categorical variables and as median with interquartile range (IQR) for continuous variables. Associations between categorical variables and fully filled quota outcomes were analyzed using Pearson's Chi-square test or Fisher's exact test where appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for binary comparisons. Univariable and multivariable logistic regression analyses were subsequently performed to identify independent predictors associated with fully filled quotas. Variables included in the multivariable model were subspecialty category, hospital type, geographic region, metropolitan municipality status, placement type, examination period, and study period. Model discrimination was assessed using receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) calculations, while calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test. Collinearity diagnostics were assessed using variance inflation factor (VIF) analysis. Statistical significance was defined as a two-sided p-value <0.05.[6,7]

All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 503 placement records comprising 757 opened quotas were analyzed during the study period. Overall, 518 quotas were filled, whereas 239 remained vacant, corresponding to an aggregate fill rate of 68.4%. Most placement records were from spring examination periods (95.0%) and initial placements (67.4%). Surgical oncology constituted the largest proportion of subspecialty placements (41.4%), followed by critical care (24.3%) and gastrointestinal surgery (23.3%). The majority of quotas were concentrated in university hospitals (70.6%), metropolitan municipalities (90.3%), and the Central Anatolia region (36.6%). Baseline characteristics of the placement records are summarized in Table 1.

Table 1. Baseline characteristics of placement records (n=503)

Variable	n (%)
Examination period	
Spring	478 (95.0)
Fall	25 (5.0)
Placement type	
Initial placement	339 (67.4)
Additional placement	164 (32.6)
Subspecialty	
Surgical oncology	208 (41.4)
Gastrointestinal surgery	117 (23.3)
Critical care	122 (24.3)
Hand surgery	46 (9.1)
Other	10 (2.0)
Hospital type	
University hospital	355 (70.6)
Training and research hospital	79 (15.7)
City hospital	69 (13.7)
Geographic region	
Marmara	99 (19.7)
Central Anatolia	184 (36.6)
Mediterranean	76 (15.1)
Aegean	65 (12.9)
Eastern Anatolia	58 (11.5)
Black Sea	11 (2.2)
Southeastern Anatolia	10 (2.0)
Metropolitan municipality	
Yes	454 (90.3)
No	49 (9.7)
Study period	
2015-2019	193 (38.4)
2020-2025	310 (61.6)
Quota outcome	
Fully filled	333 (66.2)
Not fully filled	170 (33.8)
Continuous variables	**Median (IQR)**
Quotas opened per record	1 (1-1)
Empty quotas per record	0 (0-1)
Fill rate per record (%)	100 (0-100)
Aggregate totals (2015-2025)	
Total quotas opened	757
Total quotas filled	518
Total empty quotas	239
Overall fill rate (%)	68.4

Each record represents one quota allocation in a single examination-subspecialty-hospital combination. IQR: Interquartile range

Marked temporal variation in quota distribution and occupancy rates was observed throughout the study period. Between 2015 and 2019, 319 quotas were opened, with an aggregate fill rate of 82.8%. In contrast, during the 2020-2025 period, the number of opened quotas increased substantially to 438; however, the fill rate declined markedly to 58.0%. This expansion coincided with one of the sharpest declines in occupancy observed during the study period; in 2020, 187 positions were opened across 92 centers, accompanied by a fill rate of only 47.6%. Similarly, 2022 demonstrated persistently low occupancy despite high quota numbers, with a fill rate of 43.0%. Record-level analysis demonstrated that fully filled quota rates decreased significantly from 81.9% in 2015-2019 to 56.5% in 2020-2025 (χ^2=34.33, p<0.001), corresponding to an odds ratio of 3.48 (95% CI: 2.27-5.35) favoring the earlier period. Annual quota distributions and fill rates are presented in Table 2 and Figure 1.

Table 2. Annual placement quotas and fill rates over the study period (2015-2025)

Year	Centers (n)	Quotas opened (n)	Empty quotas (n)	Fill rate (%)
2015	33	72	3	95.8
2016	32	44	6	86.4
2017	35	52	10	80.8
2018	43	60	3	95.0
2019	50	91	33	63.7
2020	92	187	98	47.6
2021	37	45	9	80.0
2022	82	93	53	43.0
2023	30	39	0	100.0
2024	25	27	11	59.3
2025	44	47	13	72.3
2015-2019	193	319	55	82.8
2020-2025	310	438	184	58.0
Total	503	757	239	68.4

Comparison of fully filled quota rates between study periods (record-level): 81.9% (158/193) in 2015-2019 vs. 56.5% (175/310) in 2020-2025; χ^2=34.33, df=1, p<0.001; odds ratio for full quota fill in 2015-2019 vs. 2020-2025=3.48 (95% CI: 2.27-5.35). Aggregate fill rate calculated as (opened-empty)/opened×100. CI: Confidence interval

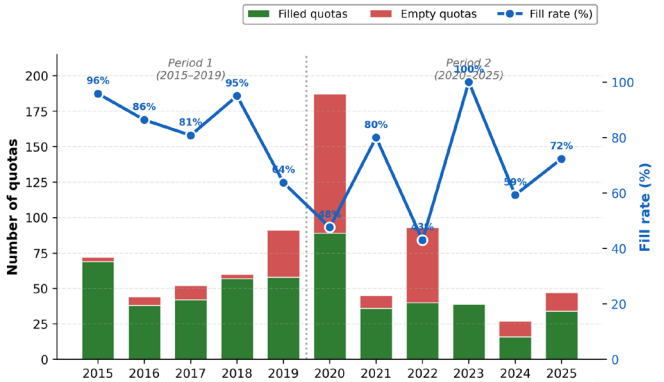

Figure 1. Annual placement quotas and fill rates over the study period (2015-2025)

Stacked bars show the absolute number of filled (green) and empty (red) quotas in each YDUS examination cycle. The blue line and right-hand axis show the aggregate fill rate for each year, calculated as filled quotas divided by total opened quotas. The dotted vertical line separates period 1 (2015-2019) from period 2 (2020-2025), the periods used for the primary comparison. Note the marked expansion of opened quotas in 2020 and 2022 with concomitant decline in fill rates

YDUS: Subspecialty Education Examination

Subspecialty-specific analyses demonstrated substantial heterogeneity in occupancy patterns. Surgical oncology and gastrointestinal surgery exhibited the highest overall fill rates at 80.6% and 75.5%, respectively. In contrast, critical care and hand surgery demonstrated considerably lower fill rates of 45.8% and 34.8%, respectively. Temporal comparisons

between study periods revealed relatively stable occupancy in gastrointestinal surgery, whereas critical care and hand surgery experienced dramatic declines after 2020. Critical care fill rates decreased from 80.4% during 2015-2019 to 18.3% during 2020-2025 (OR: 18.29, 95% CI: 7.32-45.73; p<0.001). Similarly, hand surgery fill rates declined from 80.0% to 12.9% (OR: 21.83, 95% CI: 4.64-102.69; p<0.001). Overall heterogeneity among subspecialties was statistically significant (χ^2=85.04, p<0.001). Detailed subspecialty-specific comparisons are shown in Table 3 and Figure 2.

In univariable logistic regression analyses, critical care, hand surgery, additional placement status, and the 2020-2025 study period were significantly associated with lower odds of fully filled quotas. Multivariable logistic regression analysis demonstrated that critical care (adjusted OR: 0.14, 95% CI: 0.07-0.28; p<0.001), hand surgery (adjusted OR: 0.06, 95% CI: 0.02-0.16; p<0.001), Eastern Anatolia region (adjusted OR: 0.32, 95% CI: 0.12-0.82; p=0.018), additional placements (adjusted OR: 0.14, 95% CI: 0.08-0.24; p<0.001), and the 2020-2025 period (adjusted OR: 0.13, 95% CI: 0.07-0.24; p<0.001) independently predicted lower odds of fully filled quotas. In contrast, fall examination periods were associated with higher odds of fully filled quotas after adjustment (adjusted OR: 3.19, 95% CI: 1.05-9.63; p=0.040). The multivariable model demonstrated good discrimination with an AUC of 0.865 (95% CI: 0.834-0.896) and acceptable calibration according to the Hosmer-Lemeshow goodness-of-fit test (p=0.432). Regression model results are summarized in Table 5 and Figure 4.

Table 3. Subspecialty-specific fill rates and changes between study periods

Subspecialty	Total records (n)	Total quotas (n)	Overall fill rate (%)	2015-2019 fill rate (%)	2020-2025 fill rate (%)	OR (95% CI) period 1 vs 2	p period diff
Surgical oncology	208	294	80.6	87.6	76.2	2.20 (1.01-4.78)	0.049
Gastrointestinal surgery	117	261	75.5	83.5	69.6	0.96 (0.38-2.43)	1.000
Critical care	122	144	45.8	80.0	17.7	18.29 (7.32-45.73)	<0.001
Hand surgery	46	46	34.8	80.0	12.9	21.83 (4.64-102.69)	<0.001
Other	10	12	16.7	0.0	28.6	NA	1.000

Overall heterogeneity test for subspecialty×full-fill outcome: χ^2=85.04, df=4, p<0.001. Odds ratios compare odds of full quota fill in 2015-2019 vs 2020-2025 within each subspecialty; Haldane-Anscombe correction applied for cells with low counts. p-values from Fisher's exact test. NA: Not applicable due to zero cells. OR: Odds ratio, CI: Confidence interval

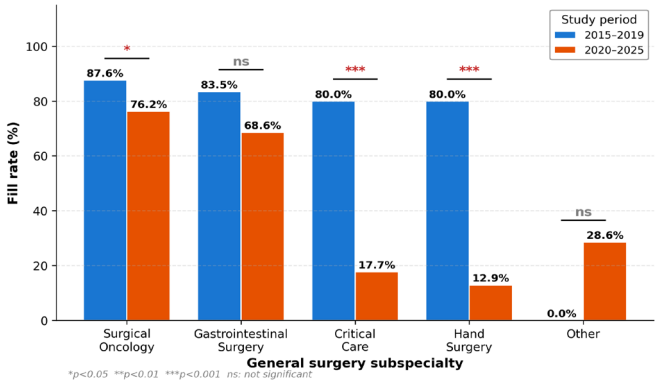

Figure 2. Subspecialty-specific fill rates across two study periods (2015-2019 vs. 2020-2025)

Aggregate fill rates (%) are shown for each general surgery subspecialty by study period. Significance markers above each pair indicate the within-subspecialty between-period difference (Fisher's exact test): ns, not significant; *p<0.05; **p<0.01; ***p<0.001. Surgical oncology and gastrointestinal surgery showed minimal change between periods, whereas critical care and hand surgery exhibited a marked decline. The "other" category (n=10 records) showed no significant change

Bivariate analyses demonstrated no significant association between fully filled quota outcomes and hospital type, metropolitan municipality status, geographic region, or examination period. However, placement type was strongly associated with quota occupancy. Initial placements demonstrated a fully filled rate of 80.2%, whereas additional placements demonstrated a markedly lower rate of 37.2% (OR: 0.15, 95% CI: 0.10-0.22; p<0.001). Detailed bivariate associations are presented in Figure 3 and Table 4.

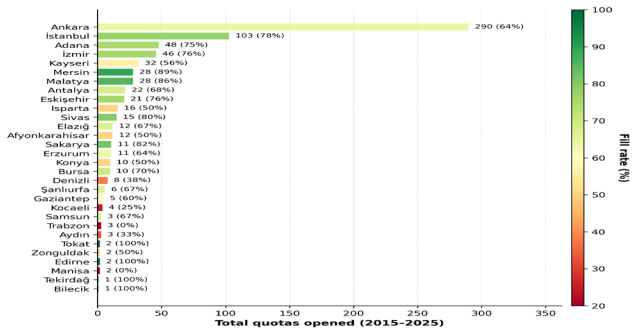

Figure 3. Provincial distribution of subspecialty quotas and fill rates, 2015-2025

Horizontal bars represent the total number of subspecialty quotas opened in each province over the study period; bar color encodes the aggregate fill rate (red-yellow-green gradient corresponds to 20-100%). Numerical labels show: total quotas (fill rate%). Quota concentration is heavily skewed toward Ankara (n=290) and İstanbul (n=103), which together account for 51.9% of all opened quotas during the study period. Substantial variability in fill rates is observed across provinces with comparable quota volumes

Table 4. Bivariate associations between study factors and fully filled quota outcome

Factor/level	n (%)	Fully filled n (%)	OR (95% CI)	p
Hospital type			-	0.684
University hospital	355 (70.6)	239 (67.3)		
Training and research hospital	79 (15.7)	51 (64.6)		
City hospital	69 (13.7)	43 (62.3)		
Metropolitan municipality (legal status)			1.40 (0.77-2.55)	0.274
Yes	454 (90.3)	304 (67.0)		
No	49 (9.7)	29 (59.2)		
Geographic region			-	0.812
Marmara	99 (19.7)	69 (69.7)		
Mediterranean	76 (15.1)	54 (71.1)		
Central Anatolia	184 (36.6)	121 (65.8)		
Aegean	65 (12.9)	40 (61.5)		
Eastern Anatolia	58 (11.5)	37 (63.8)		
Black Sea	11 (2.2)	6 (54.5)		
Southeastern Anatolia	10 (2.0)	6 (60.0)		
Placement type			0.15 (0.10-0.22)	<0.001
Initial placement	339 (67.4)	272 (80.2)		
Additional placement	164 (32.6)	61 (37.2)		
Examination period			1.58 (0.70-3.55)	0.269
Spring	478 (95.0)	319 (66.7)		
Fall	25 (5.0)	14 (56.0)		

p-values from Chi-square test or Fisher's exact test where expected cell counts <5. Reference categories: Hospital type-university; Metropolitan-no; Region-Marmara; placement type-Initial; examination period-spring. Outcome 'fully filled' indicates a quota where all positions were filled in that placement event. OR: Odds ratio (computed for 2×2 contingency only), CI: Confidence interval

Table 5. Univariable and multivariable logistic regression models for predictors of fully filled quotas

Predictor	Univariable OR (95% CI)	p	Adjusted OR (95% CI)	p
Subspecialty (ref. surgical oncology)				
Gastrointestinal surgery	0.92 (0.52-1.62)	0.780	0.83 (0.42-1.62)	0.587
Critical care	0.19 (0.12-0.31)	<0.001	0.14 (0.07-0.28)	<0.001
Hand surgery	0.13 (0.06-0.26)	<0.001	0.06 (0.02-0.16)	<0.001
Other	0.06 (0.01-0.29)	<0.001	0.02 (0.00-0.16)	<0.001
Hospital type (ref. university)				
Training and research hospital	0.88 (0.53-1.47)	0.637	0.54 (0.26-1.12)	0.097
City hospital	0.80 (0.47-1.37)	0.421	0.44 (0.21-0.95)	0.035
Geographic region (ref. Marmara)				
Mediterranean	1.07 (0.55-2.06)	0.846	0.96 (0.40-2.27)	0.918
Central Anatolia	0.84 (0.49-1.41)	0.502	0.65 (0.32-1.29)	0.216
Aegean	0.70 (0.36-1.34)	0.280	0.63 (0.26-1.55)	0.317
Eastern Anatolia	0.77 (0.39-1.52)	0.446	0.32 (0.12-0.82)	0.018
Black Sea	0.52 (0.15-1.84)	0.312	0.72 (0.10-4.99)	0.742
Southeastern Anatolia	0.65 (0.17-2.48)	0.531	0.26 (0.05-1.38)	0.113
Metropolitan municipality (ref. no)				
Yes	1.40 (0.77-2.55)	0.276	2.22 (0.90-5.48)	0.082
Placement type (ref. initial)				
Additional placement	0.15 (0.10-0.22)	<0.001	0.14 (0.08-0.24)	<0.001
Examination period (ref. spring)				
Fall	0.63 (0.28-1.43)	0.272	3.19 (1.05-9.63)	0.040
Study period (ref. 2015-2019)				
2020-2025	0.29 (0.19-0.44)	<0.001	0.13 (0.07-0.24)	<0.001

Multivariable model performance: n=503; Nagelkerke R^2=0.48; McFadden R^2=0.333; AIC=463.5; Hosmer-Lemeshow goodness-of-fit χ^2=8.01, df=8, p=0.432 (good fit); area under the ROC curve=0.865 (95% CI: 0.834-0.896); maximum variance inflation factor=1.89 (no concerning collinearity). Outcome variable: fully filled quota (yes vs no). Reference category for outcome: not fully filled. OR: Odds ratio, CI: Confidence interval, ROC: Receiver operating characteristic

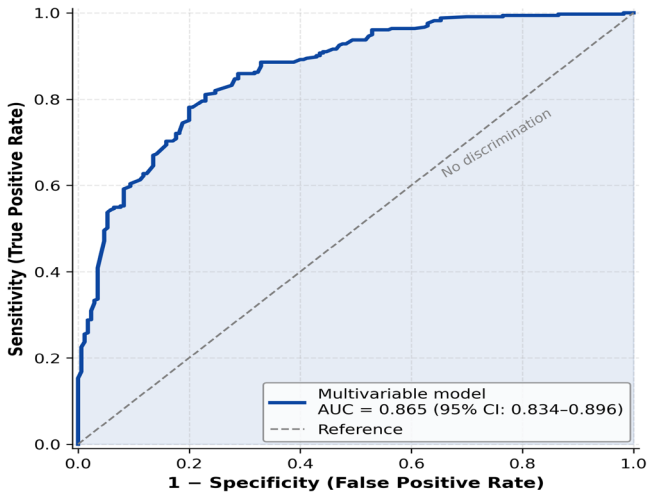

Figure 4. ROC curve for the multivariable logistic regression model predicting fully filled quotas

The model included subspecialty, hospital type, geographic region, metropolitan status, placement type, examination period, and study period as predictors. The area under the ROC curve (AUC) was 0.865 (95% CI: 0.834-0.896), indicating good discrimination. The diagonal dashed line represents the no-discrimination reference (AUC=0.5). Model fit was acceptable based on the Hosmer-Lemeshow test (χ^2=8.01, df=8, p=0.432)

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

DISCUSSION

The present nationwide analysis demonstrates that although general surgery subspecialty training quotas in Turkiye expanded substantially between 2015 and 2025, this quantitative growth was not accompanied by proportional increases in occupancy rates. On the contrary, the post-2020 period was characterized by a marked decline in fill rates despite a considerable rise in available positions. More importantly, this decline was not uniform across subspecialties. Surgical oncology and gastrointestinal surgery maintained relatively stable occupancy patterns, whereas critical care and hand surgery experienced dramatic reductions in fill rates. These findings suggest that contemporary subspecialty preferences among general surgeons are shaped not solely by numerical workforce demands, but also by broader professional, institutional, and workforce-related determinants.

One of the most striking findings of the study was the temporal shift observed after 2020. During the 2015-2019 period, overall fill rates exceeded 80%, whereas this figure declined substantially in the subsequent period despite a marked expansion in quotas. This pattern indicates that increasing the number of available positions alone may not be sufficient to sustain interest in subspecialty training. Workforce planning in surgical disciplines is inherently multidimensional and depends not only on institutional need but also on surgeons' perceptions of professional sustainability, workload, educational quality, and future career expectations.[1,2] Particularly in high-intensity specialties, growing concerns regarding work-life balance, burnout, medicolegal pressure, and declining professional satisfaction may substantially influence career decisions. Therefore, the decline observed in the present study likely reflects a broader transformation in the culture and expectations of modern surgical practice rather than a simple mismatch between supply and demand.

The pronounced heterogeneity among subspecialties further supports this interpretation. Surgical oncology and

gastrointestinal surgery demonstrated persistently high occupancy rates throughout the study period, whereas critical care and hand surgery showed dramatic declines, especially after 2020. These differences are unlikely to be explained solely by quota numbers. Instead, they probably reflect variations in perceived academic prestige, operative exposure, institutional support, lifestyle burden, financial expectations, and long-term professional identity associated with different subspecialties. Previous studies have shown that surgeons increasingly consider lifestyle-related factors and institutional working conditions when making career decisions.[2-4] Critical care, in particular, is known to be associated with high emotional stress, demanding working hours, prolonged exposure to critically ill patients, and elevated burnout risk, all of which may contribute to declining trainee interest.[1,9] Similarly, hand surgery within the general surgery pathway may suffer from limited procedural exposure and comparatively lower institutional visibility, potentially reducing its attractiveness among candidates.

Another important finding was the substantial concentration of quotas within university hospitals and metropolitan municipalities, particularly Ankara and İstanbul. Although metropolitan concentration itself was not independently associated with fully filled quotas in multivariable analysis, the overwhelming centralization of training positions indicates that subspecialty education in Turkiye remains heavily dependent on a limited number of institutional hubs. Such concentration may contribute to regional disparities in both training opportunities and future workforce distribution. Similar concerns have been reported internationally, where academic centralization and uneven distribution of subspecialty training resources have been shown to affect long-term healthcare accessibility and regional workforce balance.[10] The persistence of relatively high vacancy rates in certain geographically limited regions despite low quota numbers further suggests that geographic availability alone does not fully determine candidate preferences.

The markedly lower occupancy observed in additional placement quotas represents another critical observation. Additional placements demonstrated significantly reduced odds of full occupancy both in bivariate and multivariable analyses. This finding may indicate that many additional quotas reflect positions that are already perceived as less desirable by candidates due to institutional, geographic, or specialty-related factors. From a workforce planning perspective, repeated expansion through additional placements without addressing the underlying causes of low demand may contribute to inefficient allocation of educational resources. In this context, the present findings suggest that future subspecialty planning strategies should not rely exclusively on numerical quota expansion but should also incorporate qualitative dimensions of surgical training and professional sustainability.

From a policy perspective, these findings may help guide future subspecialty workforce planning in Turkiye. Rather than relying solely on numerical quota expansion, future planning strategies may benefit from considering specialty-specific demand, regional workforce needs, and the professional expectations of surgeons.

The increasing emphasis on burnout and physician well-being in the contemporary surgical literature further contextualizes the findings of the present study. Multiple international studies have demonstrated that burnout among surgeons and surgical trainees is associated with reduced job satisfaction, emotional exhaustion, impaired educational engagement, and even attrition from surgical careers.[1,2,9] National studies from Turkiye similarly emphasize the significant psychological and occupational burden experienced by general surgeons.[3] Therefore, declining occupancy rates in certain subspecialties may represent not merely a training issue but also an indirect indicator of broader structural stress within the surgical profession itself. In this regard, subspecialty preference trends may function as an important workforce-sensitive marker reflecting changing perceptions of professional desirability among surgeons.

The present study has several strengths. To our knowledge, this is the first nationwide study evaluating general surgery subspecialty placements in Turkiye over an extended 11-year period while simultaneously analyzing temporal trends, institutional characteristics, geographic distribution, and predictive factors associated with quota occupancy. The inclusion of regression modeling and performance analyses additionally strengthens the analytical depth of the study beyond simple descriptive reporting. Furthermore, the use of publicly accessible nationwide placement data minimizes selection bias and allows a comprehensive overview of the national subspecialty training landscape.

Limitations

Several limitations should also be acknowledged. First, the study was based on administrative placement data and therefore could not directly evaluate individual-level motivations underlying subspecialty preferences. Variables such as income expectations, academic aspirations, burnout severity, institutional culture, mentorship quality, and work-life balance perceptions were not directly measurable within the dataset. Second, occupancy rates may be influenced by external sociopolitical and healthcare-system-related factors evolving over time, including the COVID-19 pandemic, changes in healthcare policy, and broader economic conditions. Third, although the study identifies important associations, causal inferences cannot be established because of its retrospective observational design.

Despite these limitations, the findings provide important insight into the ongoing structural transformation of surgical subspecialty training in Turkiye. The observed decline in occupancy rates despite substantial quota expansion suggests that future workforce planning policies should move beyond purely quantitative approaches and incorporate the professional expectations, working conditions, and long-term sustainability concerns of surgeons. Understanding why certain subspecialties maintain strong candidate interest whereas others experience progressive decline may become increasingly important for maintaining balanced and sustainable surgical workforce planning in the coming decades. Future workforce policies that fail to account for these evolving professional realities may face increasing difficulty in maintaining a sustainable surgical subspecialty workforce.

CONCLUSION

The present nationwide analysis demonstrates that although general surgery subspecialty training quotas in Turkiye have

expanded substantially over the last decade, this quantitative growth has not been accompanied by proportional increases in occupancy rates. The marked decline in fill rates observed after 2020, particularly in critical care and hand surgery, suggests that subspecialty preferences are shaped not only by workforce demand and quota availability but also by broader professional and institutional determinants, including workload, burnout, training environment, career sustainability, and quality of life. The considerable concentration of quotas within metropolitan and university-based centers further highlights the ongoing institutional and geographic centralization of subspecialty training. In addition, the persistently low occupancy rates observed in additional placement quotas suggest that numerical expansion alone may be insufficient to address workforce needs when underlying professional expectations and structural concerns remain unresolved. Taken together, these findings indicate that future subspecialty workforce planning strategies in Turkiye should move beyond purely quantitative quota-based approaches and adopt a more comprehensive framework that incorporates educational quality, professional well-being, institutional sustainability, and surgeons' evolving career expectations. Understanding the factors driving differential subspecialty preferences may become increasingly important for maintaining a balanced, sustainable, and resilient surgical workforce in the coming years.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this study was conducted using publicly available, anonymized, and non-identifying administrative data obtained from the official ÖSYM database, ethical committee approval was not required.

Informed Consent

Since the study was conducted without the participation of any living being, no written consent form was obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

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Effects of chromosomal heteromorphisms on reproductive health

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ABSTRACT

Chromosomal heteromorphisms (CHs) are structural chromosomal variants that are generally regarded as benign. This study will examine the potential impact of CHs on reproductive health, including infertility, recurrent pregnancy loss, spermatogenesis, oogenesis, and assisted reproductive techniques technologies. A narrative review of published studies evaluating the prevalence, biological mechanisms, and reproductive implications of CHs was conducted. Although CHs are traditionally regarded as normal cytogenetic variants, several studies have reported increased frequencies among individuals with infertility, recurrent pregnancy loss, and abnormal reproductive outcomes. Proposed mechanisms include alterations in meiotic chromosome pairing, chromatin condensation, gene regulation, and genome stability. However, findings remain inconsistent across studies. Current evidence suggests a possible association between CHs and adverse reproductive outcomes; however, a definitive causal relationship has not been established. Further prospective studies are required to clarify their clinical significance.

Keywords: Chromosomal heteromorphism, chromosomal polymorphism, infertility, recurrent pregnancy loss, assisted reproductive technologies

INTRODUCTION

The term heterochromatic chromosomal variants, also known as "chromosomal heteromorphism" (CH), is used interchangeably with polymorphism or normal variant. Common cytogenetic polymorphisms identified through G-banding are considered heteromorphisms.[1] The most common variations are quantitative or positional changes in the structural DNA heterochromatin found in the centromeric regions of chromosomes 1, 9, and 16, on the long arm of the Y chromosome, and on the short arms of acrocentric chromosomes (Figure 1). These changes, known as secondary contraction regions, can involve various length patterns such as qh+ or qh- for heterochromatin blocks or may include an inversion of an entire block.[2] An increase or decrease in the short arm length of acrocentric D and G group chromosomes is called 'p±'. Meanwhile, changes in the satellites and stalks of the short arms are referred to as 'ps+/-' and 'pstk+/-', respectively (Table).[3,4]

Pericentric inversion of chromosome 9 is one of the most common chromosomal variations observed in humans.

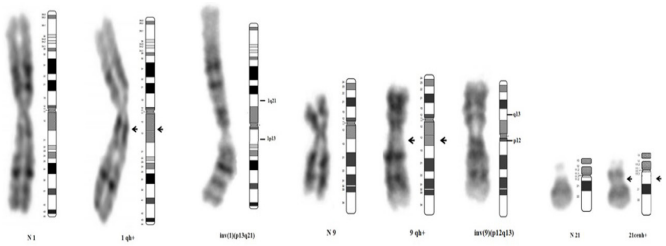

Figure 1. An increase in the long arm heterochromatin of chromosomes 1 and 9, as well as inversions considered as normal variants, are observed in chromosome 21's centromeric heterochromatin increase. The relevant regions are marked with black arrowheads (Images are taken from the archive of the Department of Medical Genetics at Başkent University)

Epidemiological data suggest its occurrence ranges from 1% to 4%. The latest version of the International System for Human Cytogenetic Nomenclature (ISCN) designates inv (9) (p12q13) as a chromosomal polymorphism with no known clinical significance (Figure 1).[3,4]

DNA sequencing and analysis of human chromosome 9 reveal that it contains the largest autosomal heterochromatin block

Table. Common chromosomal polymorphisms and banding techniques (ISCN, 2024)[38]

Method	Chromosome											
	1	2	3	9	10	13	14	15	16	21	22	Y
C-bant (+)*	qh+			qh+					qh+			q12
NOR-bant (+)						p12	p12	p12		p12	p12	
G-bant	inv (p13q21)	inv (p11.2q13)	inv (p11.2q12)	inv (p12q13)	inv (p11.2q21.2)				inv (p11.2q12.1)			inv (p11.2q11.2)

*Structural heterochromatin at the centromere is found on all chromosomes. In this table, those with frequently observed length polymorphism are included. ISCN: International System for Human Cytogenomic Nomenclature, q: Long arm, +: Increased length, qh+: The heterochromatin region on the q arm is longer than usual, NOR: Nucleolar organizer region, p: Short arm, inv: Inversion

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and is structurally highly polymorphic and heteromorphic in 6-8% of human cases. Some studies have suggested associations between the inv (9) (p12q13) variant and a range of phenotypes, including recurrent pregnancy loss, intrauterine growth retardation, heart disease, amenorrhea, Down syndrome, and sexual development disorders.[5-8]

Structural heterochromatin comprises parts of the genome that are consistently highly dense and transcriptionally inactive. These regions typically contain few genes and are made up of repetitive tandem sequences. Regions rich in structural heterochromatin, like subtelomeric and pericentromeric areas, are often conserved across individuals of the same species. In humans, the size of the subcentromeric regions on chromosomes 1, 9, and 16, as well as the distal q arm of chromosome Y, can vary significantly among individuals (**Figure 2**). Most of the time, these types of variants are stable and inherited across generations.[9]

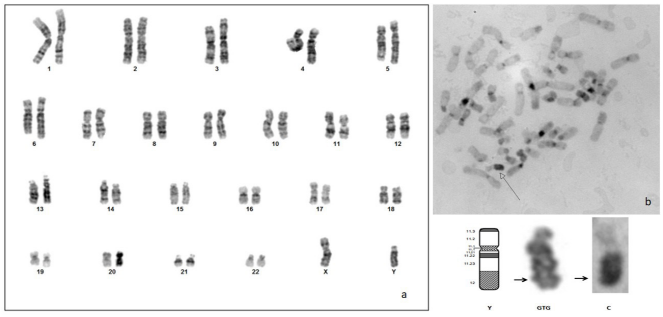

Figure 2. Karyotype (a), C-banding (b), and partial karyotype image related to length polymorphism of heterochromatin on the long arm of the Y chromosome. The Y chromosome variant is marked with an arrow in metaphase (Images are taken from the archive of the Department of Medical Genetics, Başkent University)

For a long time, structural heterochromatin was considered small chromosomal rearrangements lacking clear coding potential and not linked to abnormal phenotypes. However, some studies suggest a potential link between CH and cancer and reproductive issues. High rates of CPM have been especially observed in patients with primary infertility and recurrent pregnancy loss. Some research indicates that CHs are independently connected to the formation of multinucleated embryos,[10] and male CHs are associated with increased early pregnancy loss and decreased live birth rates after in vitro fertilization (IVF).[11] Some studies have reported that CH has no effect on IVF.[12,13]

It has been demonstrated through some studies that chromosomal heteromorphisms (CHs) in humans may have indirect effects on processes such as gametogenesis, meiotic division, and chromosome pairing in terms of reproductive health. In this context, the potential role of CH in infertility, sperm parameters, recurrent pregnancy losses, and the success of assisted reproductive techniques (ART) is noteworthy. In this review, the definition of CH, its common types, possible mechanisms of effect on reproductive functions, and the existing literature data will be examined.

Chromosomal Heteromorphisms (CHs)

CHs are microscopically visible variations involving heterochromatic segments. They are usually inherited and are most commonly observed in the pericentromeric regions of chromosomes 1, 9, and 16, as well as on the long arm of the Y chromosome. CHs are generally regarded as normal variants, and many clinical cytogenetic guidelines consider them to be of limited clinical significance.[14]

Although CHs are generally considered benign, the underlying etiological mechanisms behind some of the correlations with various diseases shown in different studies have not yet been fully understood; however, scientific research suggests that CHs may have a potential effect on genome stability and modulation. Hypotheses suggest that CHs may influence gene expression by regulating or inhibiting specific genes through position effect modifications on meiotic chromosome pairing and segregation, thereby affecting genome organization.[14]

Recent research indicates that heterochromatin associated with CHs can suppress or silence gene expression through interactions between heterochromatin and euchromatin. In different organisms, euchromatic genes located near pericentric heterochromatin show position-effect variegation, causing gene silencing in some cells where expression would typically occur, thus producing a mosaic phenotype. This phenomenon has been observed in models involving *Drosophila*, yeast, and mice.[15] Other studies also indicate that heterochromatin at centromeres is crucial for cell division. Mutations in these chromatin regions, along with defects in centromere function and cohesion, can cause problems like improper homologous chromosome pairing and disrupted cell division, potentially impacting the development of functional sperm.[4]

The impact of chromosomal polymorphisms on fertility is still not fully understood. Some studies suggest various possible mechanisms for specific types of pericentric inversions. One possibility is that the inversion could disrupt homologous chromosome pairing during meiosis. Another proposed mechanism is the interchromosomal effect. This suggests that inv (9) can affect how other chromosomes pair, since the unpaired segments of homologous chromatids might also impact other bivalent chromosomes.[16]

As seen, recent developments in molecular genetic methods have begun to reveal that DNA in heterochromatin regions possesses partial genetic functionality. Clinical observations indicate a link with several reproductive health issues, including male infertility, recurrent spontaneous miscarriages, reduced sperm quality, fetal anomalies, and disturbances in male reproductive development.[17]

Chromosomal Heteromorphisms (CHs) and Recurrent Pregnancy Loss

Repeated pregnancy loss (RPL) refers to experiencing two or more pregnancy losses before the 20th week of gestation. Female with a history of RPL have been reported to have partners exhibiting a higher incidence of sperm DNA damage compared to those without such a history.[18] The increased frequency of CHs observed in men may suggest a potential influence on chromosomal pairing and meiotic progression. Consequently, CHs may contribute to unexplained sperm DNA damage observed in some patients with RPL.[18]

In a particular study, it was observed that patients experiencing RPL exhibit a higher prevalence of CH (8-15%) compared to those with natural pregnancies (3-10%).[18,19] In a different study, it was reported that the prevalence of spontaneous abortion and preterm delivery was markedly increased in infertile female carrying CHs compared with female with

a normal karyotype. In patients experiencing unexplained recurrent pregnancy loss, CH variants such as 1qh+, inv (9), and 21 ps (s)/pstk (stk) have been reported more frequently.[18]

It is well understood that heterochromatin within chromosomes, the attachment of spindle fibers to chromosomes, the movement of chromosomes along spindle fibers, the meiotic pairing of chromosomes, and sister chromatid cohesion each confer specific benefits. Additionally, the short arm of acrocentric chromosomes also comprises heterochromatin. Any deviation exceeding acceptable limits in this region is believed to potentially result in improper chromosome segregation during karyokinesis, which may lead to RPL.[20]

Karaca et al.[21] discovered that the most common heteromorphism among female with recurrent miscarriage, infertility, and the control group is 1qh+. Additionally, they observed that female experiencing IVF failure exhibit higher frequencies of 21 chromosome variants in comparison to 1qh+. The study also found that Yqh+ was the most common heteromorphism in men within both the control and infertility groups, while Yqh- was observed in the recurrent miscarriage and IVF failure groups.

In female individuals, the chromosome 9 qh+ CH variant has been associated with an increased risk of pregnancy loss and infertility. Furthermore, the ps+ variants are predominantly observed on chromosomes 21 and 22, as well as on chromosomes 14 and 15. These variants might potentially lead to errors during meiotic segregation, resulting in reproductive failures, such as recurrent miscarriages and infertility issues, which have been highlighted in various studies.[22]

Although Karaca et al.[21] reported in their study that there is no relationship between heteromorphisms and recurrent miscarriages, Zhu et al.'s[23] study found that chromosomal polymorphic variants may negatively affect fertility. Furthermore, the unusually high frequency of acrocentric chromosome D/G group variants in female with RPL indicates that CH variants may be associated with RPL.[24]

In a study conducted by Rawal et al.,[25] elevated occurrences of satellite chromosome segments were observed in female experiencing spontaneous miscarriage and their partners. However, so far, no particular function has been identified as related to satellite segments. Nevertheless, such variations in couples may render the fetus more vulnerable to translocations, and this situation is regarded as a potential risk factor that could contribute to pregnancy loss. In the same study, patients who had experienced IVF failure and gave birth to children with malformations were also found to frequently exhibit increased centromeric heterochromatin in chromosomes 1 and 9. These variants may have contributed to mitotic instability and increased the risk of aneuploidy. Thus, heterochromatin variations in chromosomes 1 and 9 might be linked to pregnancy loss, recurrent or spontaneous miscarriages, embryonic developmental issues, and abnormal phenotypes.[25] Conversely, the research conducted by Yuan Dong et al.[26] concluded that there is no correlation between heteromorphism and reproductive failure; this conclusion is supported by the observation that heteromorphism was also present during examinations of the fathers and brothers of fertile patients. This study suggests that heteromorphisms should not be considered linked to infertility, recurrent pregnancy loss, or a history of delivering children with such conditions or malformations.

Chromosomal Heteromorphisms (CHs) and Infertility

Given the important role of heterochromatin in meiosis, it has been hypothesized that CHs may interfere with the formation of functional gametes. In CH carriers, the likelihood of embryonic aneuploidy and adverse reproductive outcomes may be increased.[2] Heterochromatin functions in polymorphic regions can suppress or inhibit gene expression, potentially affecting gametogenesis. Variations in these polymorphic chromosome regions may significantly contribute to infertility in both males and females.[27]

Chen et al.[17] reported that 14.98% of male patients attending an infertility clinic were carriers of CHs. This rate is higher than the reported prevalence of CHs in the general population.

Cheng at al.[16] study found that CHs occurred more frequently in infertile patients than in controls, with the highest rate seen in the unexplained infertility subgroup. Furthermore, the occurrence of 9qh+ was notably higher in individuals with tubal infertility, ovulation dysfunction, and unexplained infertility compared to the control group.

CH-associated heterochromatic regions are among the last chromosomal regions to complete synapsis during meiosis. It has been suggested that alterations in these regions may contribute to meiotic defects and subsequently to infertility.[15] The contribution of distinct heteromorphisms to infertility remains incompletely elucidated; however, the observation that these variants are more prevalent in infertile men than in infertile female, according to some studies, suggests that their effects may become evident during the spermatogenesis process. An unusually long heteromorphism observed in studies on infertility carriers causes the chromosome in this region to bend outward and become asynaptic during metaphase I of meiosis. This condition may contribute, at least partially, to defective spermatogenesis in some infertile men; however, these variants alone are not strongly linked to abnormal semen parameters.[9]

Chromosomal Heteromorphisms (CHs), Spermatogenesis, and Male Infertility

The literature indicates that CHs are more frequently observed in men with infertility than in female. It is thought that Y chromosome polymorphisms, accounting for nearly 20% of male chromosome polymorphisms, could be a key factor behind this discrepancy.[24]

The Yqh+ variant, characterized by an enlarged heterochromatic block on the long arm of the Y chromosome, has been proposed to contribute to chromosomal instability. This instability can disrupt the expression of euchromatin genes and the functionality of related genes, potentially affecting spermatogenesis, embryo formation, and differentiation. As a result, this condition may lead to impaired semen quality in men and fetal malformations.[28] The Y chromosome variant can lead to the deletion of heterochromatin segments near important autosomal genes (such as the AZF gene) that are crucial for gender determination and spermatogenesis. This deletion may affect gene expression or cause AZF gene microdeletions, thereby negatively impacting the production and quality of spermatogonial cells.[28]

Morales et al.[29] found that the rate of sperm aneuploidy is higher in CH carriers than in controls. It has also been shown that variation in the Y chromosome can increase the error rate in meiotic segregation and recombination. In carriers of CH with severe oligozoospermia, lower fertilization rates have been observed compared to non-carriers with severe oligozoospermia.[30] Therefore, it has been proposed that chromosomal polymorphisms may negatively impact spermatogenesis and IVF success rates.[18]

In the study by Carlos Hernandez-Nieto et al.,[2] no significant difference was found in embryo ploidy rates between CH carriers and control groups. Additionally, after accounting for patients' age and other possible confounding factors, no link was found between the presence of a CH variant and a higher risk of embryo aneuploidy.

Li et al.[31] conducted a study showing that chromosomal variants are linked to a higher risk of non-obstructive azoospermia in Chinese men. Moreover, Dul et al.[32] reported that chromosomal variants negatively impact spermatogenesis and reduce the success rates of IVF/ICSI-ET procedures.

Chromosomal Heteromorphisms (CHs), Oogenesis, and Female Infertility

Cheng et al.[16] investigated the association between CHs and female infertility and reported a higher frequency of unexplained infertility among CH carriers. In addition, female carriers may be at increased risk of adverse reproductive outcomes compared with female without CHs. Although several studies have demonstrated that CHs alone do not significantly affect embryo quality, their influence may become clinically relevant when combined with other chromosomal abnormalities. Consistent with this observation, patients carrying both chromosomal polymorphisms and translocations were found to have lower rates of high-quality embryos and higher rates of abnormal embryos than patients with translocations alone.[13,18]

Lu et al.[33] study indicated that female undergoing IVF with multiple polymorphisms and female with pstk+ variants undergoing ICSI may have an increased risk of preterm birth. The role of females CHs in increasing preterm birth risk is still unclear, and further research is needed to determine if this link is due to the negative impact of CHs on oocyte development.

Lu et al.[33] reported that CHs may negatively affect oocyte maturation. It is well established that constitutive heterochromatin plays a role in suppressing gene expression, preserving genome stability, and ensuring proper chromosome segregation.[33,34] Therefore, CHs are thought to be associated with chromosomal segregation errors and aneuploidy formation. Previous studies have shown that female carrying CHs tend to produce more aneuploid blastocysts[29] and that polymorphisms are linked to the formation of multinucleated embryos. This supports the idea that female carrying CHs might experience more meiotic errors, resulting in increased chromosomal aneuploidy in oocytes. Such errors can hinder oocyte maturation and negatively impact embryo development.[10,33]

Fewer studies have explored the link between centromeric heterochromatic variants and female infertility. However, a notable 9qh+ variant has been linked to reproductive failure. This aligns with findings that decreased recombination, especially in the oocytes of female of advanced maternal age, is associated with nondisjunction events. The impact of long heterochromatic variants on meiotic recombination in human oocytes has not been studied. If we assume they inhibit crossing over as observed in male spermatogenesis, these variants could potentially lower the overall crossing over rate in oocytes, possibly leading to fewer viable, polyploid oocytes in female of advanced maternal age.[9]

Chromosomal Heteromorphisms (CHs) and Assisted Reproductive Techniques

The impact of chromosomal polymorphisms on the results of in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) remains inconsistent. Some studies report no influence of IVF/ICSI outcomes,[2] while others suggest that CHs are linked to adverse effects.[35,36] Zhanhui Ou and colleagues,[12] in their meta-analysis, discovered that male chromosomal polymorphisms are significantly linked to reduced fertilization rates, division rates, and the percentage of good-quality embryos.

Carlos Hernandez-Nieto et al.[2] reported that CHs do not significantly affect the outcomes of assisted reproductive technologies. In another study, lower fertilization rates were reported in men carrying CHs and severe oligozoospermia compared with non-carriers who also had severe oligozoospermia. Therefore, CHs may negatively affect spermatogenesis and IVF outcomes.[35]

Although many recent publications have proposed that long heterochromatic variants could be inherited by offspring of infertile couples using assisted reproductive technologies, Wilson et al.[9] reported no statistically significant difference in the occurrence of heterochromatin variants between children conceived through these technologies and normal controls. Additionally, studies indicate that children born through assisted reproductive technology are not more likely to inherit long Y variants compared to those conceived naturally. Therefore, even if these variants play a role in infertility, children conceived through assisted methods who inherit the long Y variant are not at increased risk of negative effects from it.

A study suggests that the presence of various types of CHs can influence patients' clinical features, including IVF failure, infertility, and recurrent miscarriages. It also indicates potential interchromosomal interactions between polymorphic chromosomes and other chromosomes,[21] which may further complicate the understanding of infertility and the effectiveness of assisted reproductive technologies. Another study, after excluding individuals with complex chromosomal anomalies and clear causes of infertility, found that ICSI's impact on pregnancy outcomes depends on the gender of polymorphism carriers. Specifically, in males, carrying these polymorphisms leads to the development of poorer quality embryos.[18]

Several mechanisms have been proposed to explain the adverse effects of male CHs on ART outcomes. It has been suggested that heterochromatin on the Y chromosome's long arm might affect sperm function and that variations on the Y chromosome could lead to microdeletions and male infertility. Thus, it has been determined that chromosomal polymorphisms reduce semen quality and subsequently affect the fertilization rate.

Secondly, heterochromatin associated with chromosomal polymorphisms may potentially suppress or even silence euchromatin gene expression. Thirdly, heterochromatin clusters at the centromeres; thus, heterochromatin can lead to errors in meiotic cell division and interfere with the development of functional spermatozoa. Fourthly, structural heterochromatin mainly gathers in the telomeric, centromeric, and pericentromeric regions of chromosomes, where it stays condensed throughout the cell cycle. This organization is vital to maintaining genome stability and ensuring proper chromosome segregation. Variations in heterochromatin can disrupt these mechanisms. All of these mechanisms can affect the developmental potential of the embryo.[12]

According to Lu et al.,[33] female carrying qh+ and undergoing IVF showed higher fertilization, clinical pregnancy, and live birth rates. Another study found that female with chromosomal polymorphisms also experienced increased clinical pregnancy and live birth rates.[4] However, this study did not specifically investigate how different types of polymorphisms affect IVF and ICSI outcomes separately or analyze their distinct impacts.

Li et al.[3] in their study found that patients with inv (9) had a lower division rate in IVF compared to control patients, but no significant difference was observed when ICSI was used. Additionally, it has been reported that these patients may have a higher rate of early pregnancy loss in both ICSI and IVF groups.

In a study investigating the rate of unbalanced chromosomal rearrangements in patients with inv (9) undergoing IVF with preimplantation genetic testing (PGT-SR) prior to structural reorganization, it was found that pericentric inversions of chromosome 9 did not lead to unbalanced structural rearrangements in embryo samples on days 5/6.[3,37]

Using ICSI in men with chromosomal polymorphisms may improve fertilization rates compared to traditional IVF. Male carriers tend to lower success rates by decreasing fertilization, good-quality embryo development, clinical pregnancies, and live births, while raising biochemical pregnancy rates. In female carriers, this impact mainly manifests as a slower embryo division rate.[18]

Although several studies have reported associations between CHs and infertility, recurrent pregnancy loss, and adverse ART outcomes, the current evidence remains insufficient to support changes in routine clinical management.[2,9,33] At present, the identification of CHs should not automatically alter IVF/ICSI treatment strategies, embryo selection, or reproductive decision-making. Instead, these findings should be interpreted within the broader clinical context and considered alongside other established reproductive risk factors.

It is also important to acknowledge that reproductive outcomes may be influenced by multiple factors, including maternal age, ovarian reserve, semen quality, embryo quality, and underlying causes of infertility.[2,13,18] Therefore, the independent contribution of CHs to reproductive failure remains difficult to determine.

Future prospective studies with larger patient populations are needed to clarify the impact of specific CH variants on embryo development, implantation, pregnancy outcomes, and live birth rates.

The presence of CHs should not be considered an independent cause of reproductive failure, nor should it lead to unnecessary concern among carriers. However, given the growing body of evidence suggesting potential associations with adverse reproductive outcomes, individualized genetic counseling and careful clinical evaluation remain important. Understanding the potential implications of CHs may improve reproductive counseling, facilitate informed clinical decision-making, and support personalized management strategies for affected individuals and couples.[28] Such an approach may help ensure appropriate clinical management and comprehensive patient-centered care.

CONCLUSION

CHs are generally regarded as benign cytogenetic variants; however, they have frequently been investigated in association with reproductive failure. The potential effects of CHs on reproductive health may be explained through several proposed mechanisms: an increase or decrease in heterochromatin blocks may hinder meiotic pairing and disrupt chromatin condensation during spermatogenesis; additionally, since it contains many non-epigenetic repetitive sequences, it may affect epigenetic regulation. However, there is a noticeable inconsistency among the studies in the literature. While many studies have found an increased carrier rate, these findings do not fully establish a cause-and-effect relationship. Additionally, many studies have methodological limitations such as differences in sample sizes and control groups. Therefore, it is more accurate to state that strong prospective data is necessary for definitive classification as a risk factor. In individuals with unexplained infertility, recurrent pregnancy losses, or ART failure, the evaluation of CHs as part of conventional karyotype analysis may be considered. When emphasizing personalized genetic counseling, it is crucial to meticulously address the presence of CHs in relation to the individual's comprehensive clinical profile, and to comprehensively elucidate the potential implications.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Case Report

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Difficult airway management in a patient with mucopolysaccharidosis type IVA (Morquio A syndrome): a case report

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ABSTRACT

Mucopolysaccharidosis type IVA (Morquio A syndrome) is a rare lysosomal storage disorder characterized by glycosaminoglycan accumulation, causing progressive skeletal deformities and complex airway abnormalities that complicate anesthetic management. We report the perioperative airway management of a 27-year-old woman with MPS type IVA undergoing elective posterior cervical laminectomy for cervical myelopathy secondary to odontoid hypoplasia. Despite a preoperative Mallampati score of II, tracheal intubation was unexpectedly difficult. Attempts using both video laryngoscopy and a Macintosh laryngoscope failed because of a markedly enlarged, thickened epiglottis obstructing glottic visualization. Intubation was successfully achieved with a Miller laryngoscope. Anesthesia was maintained with total intravenous anesthesia, and the patient was extubated after complete recovery and a successful cuff leak test. Postoperative upper airway edema resolved with medical treatment. This case highlights that conventional airway assessment may underestimate airway difficulty in MPS type IVA and emphasizes the importance of alternative airway devices, meticulous perioperative planning, and vigilant postoperative monitoring.

Keywords: Miller laryngoscope, Morquio A syndrome, difficult airway

INTRODUCTION

Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome) is a rare autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS), resulting in the accumulation of keratan sulfate and chondroitin-6-sulfate in various tissues. Progressive glycosaminoglycan deposition leads to characteristic skeletal abnormalities, short stature, and a short neck, as well as severe respiratory, cardiovascular, and neurological manifestations.[1]

Airway management represents one of the greatest anesthetic challenges in patients with Morquio A syndrome, and respiratory complications remain a major cause of morbidity and mortality in this population.[1] Glycosaminoglycan (GAG) deposition within the airway results in progressive airway narrowing, while macroglossia, adenotonsillar hypertrophy, and a short neck further increase the difficulty of tracheal intubation.[2] In addition, odontoid hypoplasia and atlantoaxial instability, which are frequently encountered in these patients, substantially increase the risk of spinal cord compression and sudden death during airway manipulation requiring cervical spine movement.[1]

Previous studies have demonstrated that the incidence of difficult tracheal intubation in patients with MPS increases with age and becomes particularly pronounced in children older than 36 months.[3] Conventional airway management techniques are often inadequate because of narrowed nasal passages, limited mandibular mobility, and restricted cervical extension.[3] Therefore, perioperative airway management should be carefully planned, with alternative airway devices such as videolaryngoscopes, flexible fiberoptic bronchoscopes, and emergency tracheostomy readily available, supported by an experienced multidisciplinary team.[2,3]

In this case report, we present the perioperative management of a patient with MPS type IVA, with particular emphasis on the challenges of difficult airway management in light of current evidence and contemporary airway management strategies.

CASE

A 27-year-old woman with mucopolysaccharidosis type IV-A, weighing 18 kg and measuring 98 cm in height, was scheduled for elective posterior cervical laminectomy because of cervical myelopathy secondary to C1 dens hypoplasia. She underwent a comprehensive preoperative anesthetic evaluation. Physical examination revealed coarse facial features, hypertelorism, macroglossia, and a short neck. Neurological examination demonstrated flaccid weakness of both the upper and lower extremities. The patient had been unable to use her lower extremities since 2022 and had lost the ability to use her hands during the preceding 3 weeks.

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Cerebral angiography showed no evidence of intracranial vascular pathology, and no cardiac abnormalities were identified. Laboratory investigations, chest radiography, and electrocardiography were unremarkable. The patient was classified as American Society of Anesthesiologists (ASA) Physical Status III. Written informed consent for anesthesia and publication of this case report was obtained from both the patient and her parents.

Although the patient's Mallampati score was II, preparations for anticipated difficult airway management were made because unexpected difficult tracheal intubation may occur despite apparently reassuring bedside airway assessment, in accordance with the recommendations of the 2022 American Society of Anesthesiologists Difficult Airway Guidelines.[4] Upon arrival in the operating room, standard monitoring, including electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring, was applied, while invasive monitoring was intentionally avoided. A 22-gauge intravenous catheter was inserted into the left antecubital vein.

General anesthesia was induced with propofol (40 mg), lidocaine (10 mg), and remifentanil (60 μg), without the administration of a neuromuscular blocking agent, in order to facilitate reliable intraoperative motor evoked potential (MEP) and somatosensory evoked potential (SSEP) monitoring. Initial airway assessment using a C-MAC video laryngoscope (Karl Storz, Germany) equipped with a difficult-airway blade revealed a markedly enlarged and thickened epiglottis; however, the vocal cords could not be visualized. As an adequate glottic view could not be obtained with the video laryngoscope, direct laryngoscopy was attempted using a No. 2 Macintosh blade, but elevation of the epiglottis was unsuccessful because it remained positioned over the glottic opening. A No. 2 Miller laryngoscope was subsequently used to directly lift the epiglottis, allowing clear visualization of the glottic opening and vocal cords (**Figure**). External laryngeal manipulation using the BURP maneuver and a stylet were used to facilitate tracheal intubation, whereas a bougie was not required. Tracheal intubation was then successfully achieved using a 5.5-mm cuffed reinforced endotracheal tube.

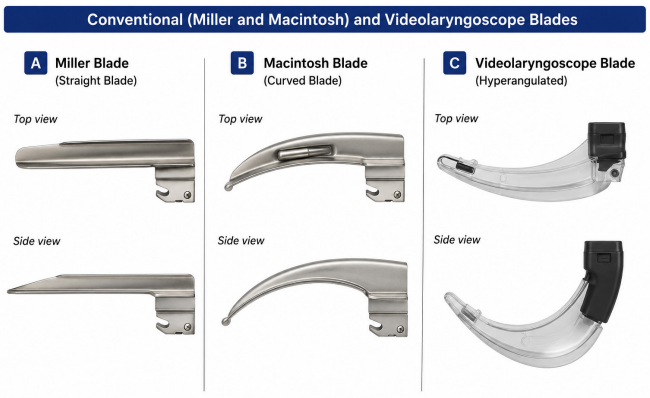

Figure. Conventional (Miller and Macintosh) and video laryngoscope blades[9]

Correct endotracheal tube placement was confirmed by bilateral chest auscultation and capnography. Anesthesia was maintained with total intravenous anesthesia (TIVA) using propofol and remifentanil. Intravenous fluids were administered at a rate of 10 ml/kg/h. At the completion of surgery, the patient was fully awake and was extubated after a successful cuff leak test.

The patient was transferred to the post-anesthesia care unit (PACU), where she was monitored for approximately 1 hour. During the early postoperative period, the patient developed upper airway mucosal edema accompanied by laryngospasm. Treatment consisted of intravenous theophylline, intravenous methylprednisolone (20 mg), and intranasal lidocaine combined with 1% diluted epinephrine. The airway symptoms resolved completely within 10 minutes without further complications, and the patient was subsequently transferred to the surgical ward after 1 hour of observation.

DISCUSSION

Mucopolysaccharidosis type IVA (Morquio A syndrome) is characterized by the accumulation of keratan sulfate within bone, cartilage, and connective tissues, leading to severe skeletal abnormalities that directly influence anesthetic management, including short stature, a short neck, odontoid hypoplasia, and consequent atlantoaxial instability.[5]

Previous studies have consistently demonstrated that airway management in patients with mucopolysaccharidoses is associated with a high incidence of difficult mask ventilation and tracheal intubation because of progressive glycosaminoglycan deposition, macroglossia, thickened supraglottic tissues, and cervical spine abnormalities.[1,3] As airway involvement progresses with age, airway management becomes increasingly challenging, emphasizing the importance of meticulous preoperative assessment, careful planning, and the availability of alternative airway devices.[3,6] Similar airway-related challenges have been reported in both pediatric and adult patients with Morquio A syndrome.[5,6]

These anatomical and pathological changes translate into a high incidence of difficult airway management in clinical practice. Previous studies have reported an incidence of difficult tracheal intubation ranging from 28% to 44% in patients with MPS.[7] As observed in our patient, progressive GAG accumulation with advancing age further increases the complexity of airway management. This observation is consistent with the 2022 ASA Difficult Airway Guidelines, which emphasize that no single bedside airway assessment reliably predicts difficult tracheal intubation and recommend comprehensive airway evaluation together with preparation for alternative airway strategies.[4]

Identification of cerebrovascular abnormalities reported in patients with MPS during the preoperative evaluation may contribute to safer perioperative management of cerebral perfusion. Although cerebral angiography is not routinely recommended, it may provide valuable information for anesthetic planning in selected patients with neurological manifestations or suspected cerebrovascular pathology.[5]

GAG deposition within the airway results in macroglossia, pharyngeal narrowing, laryngeal involvement, and thickening of the epiglottis.[5] In our case, both video laryngoscopy and direct laryngoscopy using a No. 2 Macintosh blade failed because the enlarged epiglottis could not be adequately displaced to expose the glottic opening. Although video laryngoscopy is currently recommended as a first-line technique for airway management in patients with MPS,[1,3] it may be insufficient in cases of severe soft-tissue hypertrophy, limited mouth opening, or marked epiglottic enlargement. Successful tracheal intubation was ultimately achieved using a Miller laryngoscope, suggesting that its ability to directly

elevate the epiglottis may provide a distinct advantage in selected patients with difficult airway anatomy, consistent with previous reports describing improved glottic visualization with the Miller blade in patients with a large or elongated epiglottis.[8]

Because our patient underwent surgery for cervical myelopathy secondary to odontoid hypoplasia, excessive cervical movement during airway management had to be strictly avoided. Patients with MPS IVA are at increased risk of cervical spinal cord compression and atlantoaxial instability; consequently, even minimal neck manipulation may result in catastrophic spinal cord injury or sudden death. Therefore, maintaining the cervical spine in a neutral position during tracheal intubation and considering alternative techniques, such as flexible fiberoptic bronchoscopy when appropriate, are essential components of safe airway management.

Postoperative laryngospasm and upper airway edema are well-recognized airway complications in patients with MPS. Structural airway fragility, mucosal thickening secondary to GAG deposition, and a narrowed airway lumen predispose these patients to upper airway obstruction, even following minimal airway irritation after extubation. In our patient, postoperative upper airway edema was successfully managed with prompt medical treatment, without the need for reintubation. This case highlights that safe airway management in patients with MPS extends beyond successful tracheal intubation. Extubation should be performed only after complete recovery of consciousness and airway reflexes, followed by close postoperative monitoring in an environment where airway complications can be rapidly recognized and treated.

CONCLUSION

- Laryngoscopy should be performed as gently as possible to avoid airway trauma.
- All types of laryngoscopes should be readily available to the anesthesiologist, considering the possibility that visualization of the glottic opening may be hindered by GAG accumulation.
- Clinicians should be prepared for airway edema that may develop during extubation and in the postoperative period.

Successful anesthetic management of patients with MPS type IVA requires meticulous preoperative planning, an individualized airway management strategy, and close postoperative monitoring following extubation.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

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Letter to the Editor

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Rectal ESD after prior endoscopic intervention: the impact of submucosal fibrosis on procedural success

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Keywords: Rectum, ESD, endoscopy

Dear Editor,

Endoscopic submucosal dissection (ESD) has become an important organ-preserving treatment option for large superficial rectal neoplasms, particularly laterally spreading tumors (LSTs) and lesions with suspected superficial submucosal invasion. Compared with conventional endoscopic mucosal resection (EMR), ESD provides higher en bloc and R0 resection rates, allowing accurate histopathological evaluation and reducing local recurrence risk. However, despite its clinical advantages, rectal ESD remains technically demanding, and submucosal fibrosis represents one of the most important factors limiting procedural success.[1]

Submucosal fibrosis results in loss of the natural dissection plane, reduced tissue mobility, prolonged procedure time, and increased risk of perforation. Fibrosis severity is commonly classified using the F0-F2 system: F0 indicates no fibrosis, F1 represents mild fibrosis with a white web-like appearance, and F2 indicates severe fibrosis with dense scar formation and loss of the normal submucosal layer. Severe fibrosis (F2) has been associated with lower en bloc resection rates, increased procedural difficulty, and higher risk of adverse events. In fibrotic lesions, the non-lifting sign (failure of adequate lesion elevation after submucosal injection) further compromises safe dissection by narrowing the available submucosal working space.[2]

An important consideration is that submucosal fibrosis may not solely reflect the biological characteristics of the lesion itself. Previous endoscopic interventions, including repeated forceps biopsies, incomplete resections, and inappropriate tattoo placement, may contribute to fibrosis formation and increase the technical difficulty of subsequent ESD. Although a direct causal relationship has not been definitively established for all interventions, previous manipulation of the submucosal layer has been associated with increased fibrosis and challenging dissection conditions.[3] Therefore, unnecessary interventions before referral for definitive treatment should be avoided whenever ESD is being considered.

Tattooing technique deserves particular attention in this context. While tattooing can be valuable for lesion localization, direct injection of tattoo material beneath the lesion may compromise the submucosal plane and complicate subsequent dissection. When marking is necessary, tattoo placement approximately 3-4 cm distal to the lesion using small-volume injections in multiple quadrants is preferred to facilitate localization while minimizing interference with the future dissection field.[4]

The clinical impact of fibrosis has been demonstrated in several colorectal ESD studies. In their multicenter study involving 2,423 consecutive patients undergoing colorectal ESD across 11 centers, Kamigaichi et al.[5] identified severe submucosal fibrosis as an independent risk factor for incomplete or interrupted procedures, reduced procedural success, and procedure-related complications. These findings highlight that fibrosis is not merely a technical inconvenience but a major determinant of procedural outcomes. This issue is particularly relevant in rectal ESD, where limited working space and restricted endoscope maneuverability can further magnify the challenges associated with dense fibrosis.

Current guidelines emphasize the importance of preserving the submucosal layer before definitive resection. The European Society of Gastrointestinal Endoscopy (ESGE) recommends high-quality optical diagnosis rather than routine biopsy for lesions that may require advanced endoscopic resection and supports referral to expert centers for large lesions, technically challenging locations, or cases with previous unsuccessful intervention.[4] Accordingly, a lesion considered for rectal ESD should ideally reach the expert center without unnecessary disruption of the submucosal plane.

Recent technical developments, including traction-assisted ESD and the pocket-creation method, have expanded the therapeutic options for difficult fibrotic lesions by improving visualization and maintaining a stable dissection field. However, these techniques should be considered strategies to

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overcome established fibrosis rather than methods to prevent its development. Therefore, appropriate lesion management before referral remains a fundamental component of successful ESD.[5,6]

In practical terms, large rectal lesions (particularly those ≥40 mm), lesions located near the anorectal junction, non-lifting lesions, or lesions previously subjected to biopsy, partial resection, or inappropriate tattooing should prompt early referral to experienced ESD centers. Avoiding unnecessary manipulation and preserving the native submucosal plane may increase the likelihood of en bloc R0 resection and reduce procedure-related morbidity.[4-6]

In conclusion, the outcome of rectal ESD depends not only on dissection technique but also on decisions made before the procedure begins. Preventing avoidable submucosal fibrosis through appropriate diagnostic assessment, careful tattooing practices, and timely referral may be as important as technical expertise during ESD itself.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The author declare no conflicts of interest.

Financial Disclosure

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Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

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