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Original Article

Effects of Potentially Inappropriate Medications in Older Patients with Gastrointestinal System Cancer

Gastrointestinal Sistem Kanseri Olan Yaşlı Hastalarda Potansiyel Olarak Uygun Olmayan İlaçların Etkileri

Melike OZKAN, Irfan KARAHAN, Selim YALCIN, Gozde SENGUL AYCICEK

Kırıkkale University Faculty of Medicine, Department of Internal Medicine, Kirikkale, Turkey

ABSTRACT

Objective: Potentially inappropriate medications (PIM) is a crucial problem in the geriatric population. The amount of prescription and unadherence increase because of the different problems encountered in cancer patients. Our aim was to evaluate the effects of PIM in patients with gastrointestinal system cancer and to investigate its relationship with chemotherapy side effects, mortality, and progression.

Methods: This retrospective cohort study assessed 154 patients with gastrointestinal system cancer. Demographics and disease features, the presence of PIM according to the "TIME-to-STOP" criteria and baseline laboratory parameters were recorded. The effects of PIM on survival and adverse treatment events were evaluated.

Results: 66.9% of the cases were male and 33.1% were female. The mean age was 71.9±6.4 years. The most common side effects of chemotherapy are nausea, vomiting, kidney injury, and pain. The most frequently used prescriptions among the 98 PIMs were gliclazide, hyoscine N-butylbromide, simethicone, diphenoxylate atropine, and thiocolchicoside. PIM was detected in 68.1% of the participants. Chemotherapy side effects were more common in PIM group (p<0.001, odds ratio =5.6). PIM had no effect on mortality. Factors associated with mortality were age, stage, albumin, creatinine, operation history, and progression. A significant relationship was found between age, cancer stage, albumin, creatinine, operation history, and PIM in the regression model. There was no relationship between PIM and progression-free survival.

Conclusion: Chemotherapy toxicity may increase with PIM detected on diagnosis. We suggest that PIM is an important factor in predicting the side effects of chemotherapy and minimizing the adverse effects.

Keywords: Potentially inappropriate medications, mortality, gastrointestinal system cancers, chemotherapy, TIME-to-STOP criteria

ÖZ

Amaç: Potansiyel olarak uygun olmayan ilaç kullanımı (UİK) geriatrik popülasyonun önemli bir sorunudur. Kanser hastalarında karşılaşılan farklı sorunlar nedeniyle reçete miktarı ve uyumsuzluk artmaktadır. Amacımız gastrointestinal sistem kanserli hastalarda UİK'nin etkilerini değerlendirmek ve kemoterapi yan etkileri, mortalite ve progresyon ile ilişkisini araştırmaktır.

Yöntemler: Bu retrospektif kohort çalışmada gastrointestinal sistem kanseri olan 154 hasta değerlendirilmiştir. Demografik ve hastalık özellikleri, "TIME-to-STOP" kriterlerine göre UİK varlığı ve başlangıç laboratuvar parametreleri kaydedilmiştir. UİK'nin sağkalım ve tedavinin advers olayları üzerindeki etkileri değerlendirilmiştir.

Bulgular: Olguların %66,9'u erkek ve %33,1'i kadındır. Ortalama yaş 71,9±6,4 yıl idi. Kemoterapinin en sık görülen yan etkileri bulantı, kusma, böbrek hasarı ve ağrı olarak sıralanmıştır. Toplam 98 UİK arasında en sık kullanılan reçeteler gliclazide, hyoscine N-butylbromide, simethicone, diphenoxylate atropine ve thiocolchicoside idi. Katılımcıların %68,1'inde UİK tespit edilmiştir. Kemoterapi yan etkileri UİK grubunda daha yaygındı (p<0,001, olasılık oranı =5,6). UİK'nin mortalite üzerinde etkisi yoktu. Mortalite ile ilişkili faktörler yaş, evre, albumin, kreatinin, operasyon öyküsü ve progresyon idi. Regresyon analizinde yaş, kanser evresi, albümin, kreatinin, operasyon öyküsü ve UİK arasında anlamlı bir ilişki bulundu. UİK ile progresyonsuz sağkalım arasında bir ilişki bulunmadı.

Sonuç: Kemoterapi toksisitesi tanı sırasında saptanan UİK ile artabilir. UİK'nin kemoterapinin yan etkilerini öngörmede ve olumsuz etkileri en aza indirmede önemli bir faktör olabileceğini düşünüyoruz.

Anahtar kelimeler: Potansiyel olarak uygun olmayan ilaç kullanımı, mortalite, gastrointestinal sistem kanserleri, kemoterapi, TIME-to-STOP kriterleri

Address for Correspondence: I. Karahan,
Kirikkale University Faculty of Medicine, Department of Internal Medicine, Kirikkale, Turkey
E-mail: irfan_karahan@yahoo.com **ORCID ID:** orcid.org/0000-0003-4669-1751

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INTRODUCTION

In recent years, as the quality of life has improved around the world, life expectancy has increased, leading to an increase in the geriatric population[1]. As a result, disease rates and drug use increase. Increased drug use leads to increased costs, potentially inappropriate medication (PIM) and polypharmacy. Pharmacokinetic and pharmacodynamic changes in the geriatric population and organ dysfunction that occur over time may lead to drug-related adverse effects. This suggests that reducing polypharmacy and PIM may improve the health of older patients[2]. One of the most important goals in the care of geriatric patients is to optimise the number and dosage of medications used. To this end, a clear medication list is a crucial step. The correct medication list should include matching the diagnosis to the prescription, selecting the most appropriate medication, educating the patient and carer about the patient's physiological responses, and ensuring that the medication is used as directed[3]. Another critical issue with medication among older adults is the prescription and use of PIM[4]. Various strategies have been developed to control this situation. The development of universal criteria to determine PIM is one of these methods. The most commonly used tools worldwide are the CRIME, Beers, and TIME criteria. As the CRIME and Beers criteria are based on foreign criteria, it causes various difficulties due to drugs that are not used in Turkey. For this reason, under the leadership of the Rational Drug Use Working Group of the Turkish Academic Geriatrics Society, with the wide participation of experts in their field and experienced in the clinical practice of elderly patients in Turkey, guidelines have been prepared under the names of TIME to STOP and TIME to START[5].

Cancer treatment increases drug use, health service admissions, and disease burden[6]. Therefore, a cancer diagnosis increases the risk of PIM. Being over the age of 65 years has been shown to reduce survival from gastrointestinal (GIS) cancers. It has been observed that the cause of this condition is related to malnutrition, weight loss, chemotherapy toxicity, and comorbidities[7]. Multimorbidity has been found to affect older patients undergoing cancer treatment and complicate survivor care and medical decision making[8]. Our aim in this study was to evaluate the effects of PIM in patients with GIS cancer aged 65 years and to investigate the relationship with chemotherapy side effects, mortality, and progression.

MATERIALS and METHODS

Newly diagnosed patients with GIS cancer aged 65 years who registered at the Kırıkkale University Faculty of Medicine, Department of Medical Oncology between June 2012 and June 2020 were retrospectively studied. Approval for the study was obtained from Kırıkkale University Medical Faculty Non-interventional Studies Ethics Committee (decision no: 2021.01.22, date: 04.02.2021). This study adhered to the tenets of the Declaration of Helsinki. To determine the general characteristics of the patients, age, sex, Eastern Co-operative Oncology Group performance status, smoking status, cancer diagnoses, cancer stages, comorbidities, date of diagnosis, date of death, condition at death, surgery, radiotherapy, drugs, progression status, presence of chemotherapy side effects, and type of side effects were recorded. Laboratory parameters recorded at the time of patient diagnosis, such as haemogram parameters, estimated glomerular filtration rate using the CKD-EPI formula, alanine aminotransferase, creatinine level, albumin level, C-reactive protein (CRP) and bilirubin level. The "TIME to STOP" criteria were used to identify inappropriate medications used by patients. The relationship between PIM and survival and chemotherapy side effects was evaluated according to the TIME to STOP criteria. The factors affecting progression-free survival (PFS) were examined.

The inclusion criteria were a histopathologically confirmed diagnosis of GIS cancer, age 65 or older, access to information on drugs used at the time of diagnosis, and receipt of chemotherapy. Patients with missing data were excluded.

Statistical Analysis

IBM SPSS 25 was used for all analyses. Normal distribution existence was evaluated with the help of Shapiro's Wilk test and histogram. Non-normally distributed numerical variables were given with median (minimum-maximum), normally distributed variables with mean ± standard deviation. N (%) was given for categorical variables. Fisher's Exact test or chi-square test was used for categorical group comparisons; Mann-Whitney U test or Student's t-test was used for group comparisons of numerical variables. Kaplan-Meier survival curves were used for survival analysis, and Cox regression analysis was performed. $P<0.05$ was considered significant.

RESULTS

Of the 154 patients, 66.9% were male and 33.1% were female. The mean age at application was 71.9±6.4 years. The demographics, stage, and characteristics of the cancers are shown in Table 1.

Although chemotherapy side effects were observed in 89 patients, this group represents 57.8% of our sample.

Table 1. The characteristics of the working group.		
Age, years	71 (65-90)	
Female, sex	51 (33.1%)	
Multimorbidity	Hypertension	66 (42.8%)
	Coronary artery disease	38 (24.6%)
	Diabetes mellitus	32 (20.7%)
	GERD	28 (18.1%)
	BPH	18 (11.6%)
ECOG performance score	ECOG 0-I	123 (79.8%)
	ECOG II	29 (18.8%)
	ECOG III	2 (1.2%)
	ECOG IV	0
Diagnosis	Colon cancer: 72 (46.7%)	
	Gastric cancer: 43 (27.9%)	
	Pancreatic cancer: 18 (11.7%)	
	Hepatocellular cancer: 10 (6.5%)	
	Others: 11 (7%)	
Surgical operation	124 (80%)	
Radiotherapy	15 (10%)	
Smoking	80 (52%)	
Survival	80 (52%)	
Follow up time, days	716 (14-3161)	
Cancer stage	Stage I	2 (1.2%)
	Stage II	30 (19.5%)
	Stage III	54 (35%)
	Stage IV	68 (44.1%)
PIM	106 (68.1%)	
Chemotherapy side effect	89 (57.8%)	
Progression	78 (50.5%)	

ECOG: Eastern Co-operative Oncology Group, GERD: Gastroesophageal reflux disease, BPH: Benign prostatic hyperplasia, PIM: Potentially inappropriate medications

Considering the order of the side effects observed in the patients, nausea 51 (33%), vomiting 35 (22.7%), renal toxicity 16 (10.3%), pain 9 (6%), electrolyte disturbance 7 (4.5%), oral intake disorder 5 (3%), low platelets 9 (6%), hemoglobin decrease 4 (2.5%), and neutropenia 4 (2.5%). According to the "TIME to STOP" criteria, the most frequently used drugs among the 98 inappropriate uses were gliclazide (n=10), hyosin N-butyl bromide (n=9), simethicone (n=7), diphenoxylate atropine (n=7) and thiocolchicoside (n=7). Regarding the drug groups used, the most common were anticholinergic antispasmodics (n=35), antiaggregants (n=9), non-steroidal anti-inflammatory drugs (NSAIDs) (n=9), beta-blockers (n=6) and diuretics (n=5). While 69% of men had PIM, 68.6% of women had PIM, and there was no significant difference (p=0.543).

The PIM group had a higher prevalence of chemotherapy side effects than the others (83.3% vs. 48.4%) (p<0.001, odds ratio =5.6).

The result was not significant when comparing the relationship between PIM and mortality (Figure 1). When factors associated with survival were evaluated by Cox regression analysis, they were found to be significantly associated with age, history of surgery, creatinine, albumin, advanced stage, and presence of progression (Table 2).

The log-rank test showed that PIM history had no significant effect in PFS (Figure 2). The association between PIM and progression was found to be significant. Factors associated with PFS were found to be significantly correlated with age, surgical history, disease stage, albumin, creatinine, CRP levels, and the presence of progression by Cox regression analysis (Table 3).

DISCUSSION

The study showed that PIM was common in older people with GIS cancers and that PIM could increase chemotherapy side effects and worsen PFS. Commonly used drugs, such as antidiabetics and antispasmodics, also topped the list of inappropriate drugs.

In the study conducted by Lund et al.[9] in patients with colon cancer who were 66 years old and older using 5-FU/capesitabine treatment using 2012 Beers criteria, PIM was found to be 40%. The lower PIM rate in this study can be explained by the narrow coverage of the Beers criteria. In the study conducted by Karuturi et al.[10] in the USA on patients with stage II-III colorectal cancer aged 66

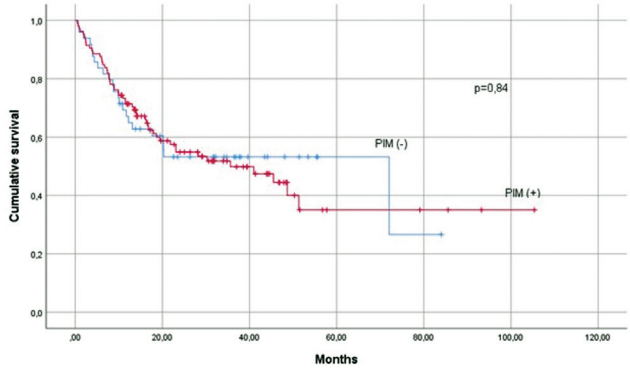

Figure 1. The comparison of survival for medication use with Log-rank test.

PIM: Potentially inappropriate medication

Table 2. Evaluation of survival related factors by Cox regression analysis.				
	Univariate		Multivariate	
	HR (%95 CI lower upper)	Significance	HR (%95 CI lower upper)	Significance
Age	1.042 (1.003-1.082)	p=0.036*	1.04 (0.99-1.01)	p=0.058
Operation history	0.33 (0.20-0.56)	p<0.001*	0.51 (0.29-0.87)	p=0.015*
Albumin level, g/dL	0.55 (0.38-0.78)	p=0.01*	0.53 (0.36-0.71)	p=0.001*
CRP* level, mg/dL	1.006 (1.002-1.010)	p=0.007*	1.005 (0.999-1.077)	p=0.095
Advanced stage	2.61 (1.78-3.83)	p<0.001*	2.21 (1.47-3.33)	p<0.001*
Presence of progression	2.62 (1.58-4.62)	p<0.001*	1.73 (1.04-2.90)	p=0.035*
Creatinine level, mg/dL	1.01 (1.001-1.010)	p=0.003*	1.01 (1.001-1.010)	p=0.007*
*Significant, CRP: C-reactive protein, CI: Confidence interval, HR: Hazard ratio				

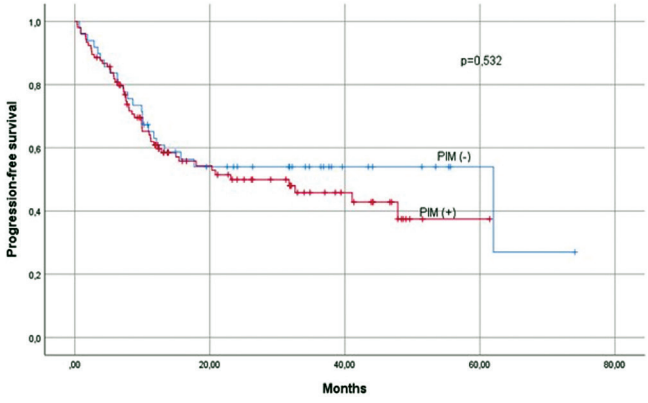

Figure 2. The comparison of progression-free survival for medication use with Log-rank test.

years and older, PIM was detected as 30.9%. This may be because the study was based on drug-related side effects of the patients in the sample and considered them as inappropriate drugs. Similar to our study, PIM was found to be 68.4% in a study conducted by Feng et al.[8] in Japan using the 2015 Beers criteria in patients with colon cancer aged 70 years. In a study conducted in Sweden between 2007 and 2010, in 7279 patients with colorectal cancer aged 75 years and over, according to the National Board of Health and Welfare criteria, the PIM was found to be 22.5%[11]. The National Board of Health and Welfare criteria are used in Sweden for patients aged 75 years and over to reduce the pharmacological burden of physicians, prescribe medication in the correct indication, and prevent the prescribing of an inappropriate drug[12]. The reason why PIM was found to be lower than our result in this study may be that the criteria applied are limited and the drugs that directly affect mortality are considered inappropriate. There is no study evaluating general GIS cancers in the literature. In this respect, our study can be considered the first to our knowledge. Similar to our study, 65.2% of PIM patients evaluated with STOPP criteria were found in the study conducted by de Agustín Sierra et al.[3] in Spain at the age of 80 years and above. In the study conducted by van Loveren et al.[6] in 2019 in 150 patients diagnosed with cancer aged 65 years and older in the Netherlands, PIM was detected in 49% of patients using the STOPP criteria. Differences in measurement methods evaluating PIM or the fact that the patient groups included in the studies are not similar may explain the variability in the PIM prevalence results.

The fact that the most commonly used drugs are antihyperglycemic and antispasmodic drugs with anticholinergic effects can be explained by the high incidence of diabetes and gastroesophageal reflux disease in our population. In a study conducted by Lund et al.[9] using Beers criteria of colon cancer patients receiving 5-FU/capesitabine, they found that the most frequently used inappropriate drugs were metoclopramide and promethazine. The aspects that differ from our study are that while this study investigated the frequency of inappropriate use of cancer-related drugs at any time after diagnosis, our study investigated the drugs used inappropriately by newly diagnosed cancer patients. Therefore, drugs used for complications related to cancer treatment in other studies in the literature constitute the majority of inappropriate uses. In a study by Yayla et al.[13], PIM was determined to be 14.8% according to STOPP version 1 criteria. It was observed that the most commonly used drugs were NSAIDs, and acetylsalicylic acid was the second most common. The limitations of this study may be the inadequate STOPP version 1 criteria and the dispersion of the patient population. Therefore, it can be assumed that the percentage of NSAID uses in the population has increased. In Spain, the five most commonly used drugs among the PIM using STOPP criteria at the age of 80 years and above are lorazepam, furosemide, risperidone, lormetazepam,

Table 3. Evaluation of factors associated with progression-free survival by Cox regression analysis.				
	Univariate		Multivariate	
	HR (%95 CI lower upper)	Significance	HR (%95 CI lower upper)	Significance
Age, years	1.02 (0.98-1.06)	p=0.1	1.04 (1.006-1.09)	p=0.025*
Operation history	0.32 (0.19-0.54)	p<0.001*	0.46 (0.26-0.79)	p=0.005*
Advanced stage	2.52 (1.77-3.63)	p<0.001*	2.26 (1.51-4.20)	p<0.001*
CRP* level, mg/dL	1.007 (1.003-1.011)	p=0.001*	1.005 (1.001-1.010)	p=0.028*
Albumin level, g/dL	0.59 (0.41-0.84)	p=0.004*	0.58 (0.38-0.87)	p=0.01*
Creatinine level, mg/dL	1.001 (1.001-1.010)	p=0.003*	1.001 (1.001-1.010)	p=0.01*
*Significant, CRP: C-reactive protein, CI: Confidence interval, HR: Hazard ratio				

and bromazepam[3]. Frequent use of the benzodiazepine group was thought to be associated with an increase in sleep disturbance and neuropathic pain over the age of 80 years. Similar to this study, in the study conducted by Hakozaki et al.[14] in patients with lung cancer in Japan, the most commonly used drug was benzodiazepine. This was explained by increased pain during cancer treatment, sleep disturbance, and the high frequency of benzodiazepine use in Japanese. The reason for the different results in studies using the STOPP or Beers criteria is probably because of the prescribing practice characteristics between countries and the different drug ingredient forms available in the market[15].

The high risk of adverse drug reactions in older adults due to pharmacokinetic and pharmacodynamic changes increases the risk of PIM[8]. Chemotherapy toxicity was detected in more than half of the patients in our study. There was a significant increase in chemotherapy side effects among patients using inappropriate drugs. In a study conducted by Hong et al.[16] in 301 patients aged 70 years and older with cancer, no significant relationship was found between chemotherapy-related toxicity and PIM. The reason may be that the patients included in the study had end-stage cancers and the type was not specified, the use of the more limited Beers criteria, and other risk factors affecting chemotherapy-related toxicity. No significant relationship was found between PIM and chemotherapy toxicity in the study by Karuturi et al.[10]. The limitations of this study are that it uses a narrow list of criteria for PIM detection. In a study by Maggiore et al.[17] in the USA, in which the 2012 Beers criteria were used in cancer patients aged 65 years and over, evaluating the possibility of PIM to predict chemotherapy toxicity, these two variables were found to be unrelated. In a study conducted in 301 patients aged 70 years with cancer in Korea between 2014 and 2015, no significant relationship was found between chemotherapy-related toxicity and PIM[16]. This can be explained by the fact that the cancer diagnosis of the patients included in the study was a heterogeneous group. Another study revealed that the relationship between PIM and chemotherapy toxicity was insignificant[18].

In our study, it was determined that PIM could be a helpful factor in predicting cancer progression, supporting these results. No study that investigates the relationship between PIM and cancer progression has been found in the literature.

In our study, we observed the presence of progression, which stands out as the most important parameter among the factors affecting mortality. Similar to our study, a significant relationship was found between recurrence and survival in a study conducted in patients with esophageal cancer[19]. 48% of the patients in our population died within 7 years. In the study by Karuturi et al.[10] on patients with colorectal cancer, the 1-year mortality rate was determined to be 5%. The reason for the high mortality rate in our study may be the advanced stages among the patients and the long follow-up period. In our study, the unsignificant relationship between age and mortality had low reliability. This can be explained by the fact that there are too many factors affecting mortality and the small number of our patients. In other studies, a positive correlation was found between the age and stage of the patients with mortality, which supports this situation[20]. In a study conducted in Sweden in patients with colorectal cancer aged 75 years and older, being 81 years and older was among the criteria that significantly increased mortality[11].

In our study, high serum creatinine and low serum albumin levels were associated with mortality. The close relationship between serum albumin level and mortality is supported by many studies conducted worldwide[19]. In this study, 80% of the patients included underwent surgery for cancer. Surgical operation was associated with increased survival. The reason for the lower mortality in patients undergoing surgery may be that

patients diagnosed at an early stage undergo surgical operations and the chances of being cured by surgery increase. Similar to our study, the literature also supports this situation[21].

The relationship between PIM and mortality was insignificant. The reason for this situation may be that there are too many criteria affecting mortality in cancer patients and the distribution width of the patients is widespread. As in our study, no study was found in the literature comparing inappropriate drug use and mortality in all patients with GIS cancer. PIM was found to be effective in increasing mortality in a study conducted in patients aged 75 years and older with colorectal cancer, one of the GIS cancers[11]. The reason may be that the first 30-day postoperative mortality was examined in the study and the drugs that lead to conditions that directly affect mortality, such as delirium and falls, were considered inappropriate. Similar to our study, in the study conducted by Hakozaki et al.[14] in patients with lung cancer in Japan, no significant relationship was found in the comparison of PIM and mortality.

In the study of Matsuda et al.[19] in patients with esophageal cancer in Japan, a significant relationship was found between PFS and albumin level. This study supports our view that albumin level is an important predictor of PFS. In a study by Willegger et al.[22] in patients with sarcoma, PFS was found to be associated with decreased albumin, whereas the creatinine relationship was found to be insignificant. It was thought that this situation might be due to the difference in our study sample. In addition, we did not find any association between PFS and PIM.

This study has several limitations. A retrospective evaluation may reduce the strength of the analyses. In addition, the TIME to START criteria could not be used due to missing data. The sample size was small and limited to a single center. Only newly diagnosed patients and the snapshot at diagnosis were analyzed. Information on herbal and over-the-counter medicines is limited. There was a lack of information on the onset times and grades of adverse effects. A lack of comprehensive geriatric assessments. Although the TIME to STOP criteria include some suggestions about medications with cancer treatment, there is no specific cancer treatment. However, to the best of our knowledge, this is the first study to assess PIM in cancer patients using these criteria in our population.

CONCLUSION

We believe that our study contains important data as it provides an idea of the PIM profile of the elderly in our country and will shed light on future multicenter and comprehensive studies. The current criteria for evaluating the use of PIM were developed for the general adult population and do not consider the geriatric oncology population. This study shows that these measures need to be improved for optimal use in settings specific to oncology patients.

We also found that chemotherapy toxicity increased with PIM detected at the time of cancer diagnosis. This situation indicates that considering PIM may help to predict chemotherapy side effects. Further studies are needed to evaluate PIM during the cancer treatment continuum and in palliative care.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Kırıkkale University Faculty of Medicine Non-interventional Studies Ethics Committee (decision no: 2021.01.22, date: 04.02.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: S.Y., G.S.A., Concept: S.Y., G.S.A., Design: I.K., G.S.A., Data Collection and/or Processing: M.O., S.Y., Analysis and/or Interpretation: I.K., G.S.A., Literature Search: M.O., S.Y., Writing: M.O., I.K.

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