Sex Differences in Outcomes of Hepatobiliary and Pancreatic Surgery with Accelerated Rehabilitation

Ann. Ital. Chir., 2024 95, 2: 166–173
https://doi.org/10.62713/aic.3169

Xinxin Zhang[1], Qian Wang[2], Min Zhang[3], Liguang Chen[1], Danhong Peng[3]

[1]Hepatobiliary and Pancreatic Surgery, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China
[2]Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China
[3]General Surgical Ward, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China

Background: Sex, in the sense of gender, is a major social demographic characteristic that has been shown to affect health care outcomes. The concept of enhanced recovery after surgery (ERAS) is an effective perioperative management measure that can reduce the perioperative stress response in patients. However, there are few studies on the differences between male and female patients under this type of care. We aimed to analyze sex differences in clinical characteristics among patients undergoing hepatobiliary and pancreatic surgery with accelerated rehabilitation.

Methods: We enrolled patients who underwent liver, biliary tract, and gallbladder operations in the Department of Hepatobiliary and Pancreatic Surgery of Taizhou Hospital, Zhejiang Province, China, from April 2021 to July 2021. Key measures were collected for patients undergoing perioperative accelerated rehabilitation (i.e., the case group). The study group was assembled by performing 1:1 matching for age, sex, chronic disease, and type of surgery. Postoperative risk assessment, postoperative recovery indicators, and postoperative length of hospital stay (days) were compared between male and female patients.

Results: A total of 226 surgical patients were enrolled, including 109 male (48.23%) and 117 female patients (51.77%). The outcomes, presented as the median (min, max), were as follows: pulmonary rehabilitation risk assessment in females (1(0,3)) and males (0(0,2)), postoperative nausea and vomiting in females (2(1,3)) and males (1(0,2)), and time to first defecation in females (31(4,61)) and males (36(10,78)). Significant differences were indicated by p values < 0.05.

Conclusion: We identified sex differences in the clinical prognosis and performance of perioperative patients undergoing hepatobiliary and pancreatic surgery with accelerated rehabilitation. The perioperative pulmonary rehabilitation risk of male patients was higher than that of female patients, and the time to first defecation was longer in male than in female patients. The incidence of nausea and vomiting in women was higher than in men.

Keywords: accelerated rehabilitation surgery; hepatobiliary and pancreatic surgery; sex differences

Introduction

The concept of enhanced recovery after surgery (ERAS) was first proposed by Danish Professor Kehlet [1] in 1997 using evidence-based medicine, in which perioperative measures can be optimized to reduce physical and psychological stress responses in patients, thus reducing complications, shortening their hospital stay, and accelerating patient rehabilitation. ERAS represents a shift in perioperative philosophy; it reduces postoperative complications and the length of hospital stay, improves postoperative quality of life, and reduces overall health care costs [2]. In orthopedic, gynecologic, cardiothoracic, and gastrointestinal surgery, ERAS has reduced hospital stays without increasing readmission rates [3].

Correspondence to: Danhong Peng, General Surgical Ward, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China (e-mail: pengdanhong2018@163.com).

Biological sex, which is defined by characteristics encoded in DNA, body chemistry, and other physical factors, and gender, the collection of social, cultural, behavioral, and psychological traits that are a function of being a human male or female, influence both health and disease. Differences in health care delivery and outcome between men and women have been documented in many areas of research, including lung disease [4], stroke [5], kidney transplantation [6], lumbar discectomy [7], and pancreatic cancer [8]. Identifying these differences is crucial in not only optimizing health care outcomes but also minimizing existing disparities in access to care [9]. Herein, we will use the term "sex" to refer to the trait of being male or female, even though we do not address whether the differences we observed are caused by solely physical, solely social, or a combination of both types of factors.

Until now, most studies on ERAS have focused on the hospital length of stay, readmission, and postoperative complications. A set of ERAS-specific core outcomes have been

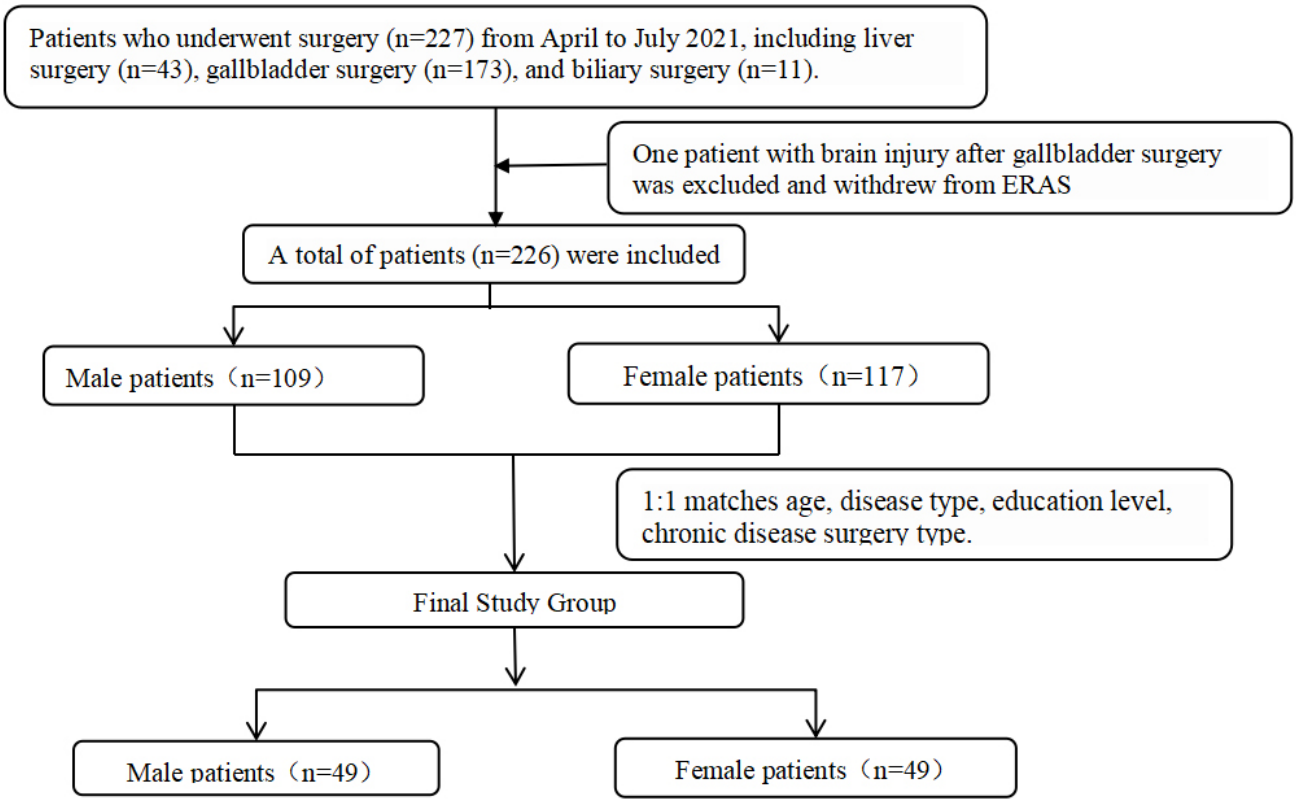

Fig. 1. Sample selection. ERAS, enhanced recovery after surgery.

developed to assist in homogeneous outcome reporting in ERAS studies [10]. After the implementation of these key measures in the ERAS perioperative period, however, few studies have investigated whether there are sex differences in outcomes. Therefore, in this study, we analyzed the outcomes of perioperative ERAS key measures in both male and female patients.

Materials and Methods

Methods

This study was approved by the Ethical Committee of Taizhou Hospital of Zhejiang Province (number K20220129). The inclusion criteria were: patients undergoing elective surgery; age ≥18 years; able to move and communicate; and complete clinical data available. The exclusion criteria were: postoperative complications; perioperative conditions that were life-threatening; organ failure; and patients who died during surgery. After exclusion, a total of 226 patients who met the inclusion criteria for elective surgery in Taizhou Hospital, Zhejiang Province from April to July 2021 were reviewed and subjected to the ERAS clinical pathway. In order to eliminate bias and help balance the differences in baseline characteristics and perioperative assessments between the two groups, the study group was formed by performing 1:1 matching for age, sex, chronic disease, and type of surgery. Finally, we enrolled 49 men and 49 women in the study group, as shown in Fig. 1.

Procedure

ERAS Team

A multidisciplinary ERAS team was established, including hepatobiliary and pancreatic surgeons and staff from the nursing department, mental health department, anesthesiology department, rehabilitation department, nutrition department, respiratory department, operating room, radiology department, and other departments.

ERAS-specific Implementation Plan

After diagnosis, a physician issued each patient a certificate of hospitalization and preoperative examination and provided them with the "Accelerated Rehabilitation Surgery Education Manual" as revised by the Department of Hepatobiliary and Pancreatic Surgery of Taizhou Hospital. The patients underwent preoperative visits in the outpatient department of anesthesiology and nutrition. Specialized nurses in each department communicated with patients, extracted patient data from the hospital information system (HIS), and conducted telephone interviews. These nurses tried to understand the patient's diet, activities, sleep, psychology, and other home life-related factors, and gave relevant professional guidance to improve the patient's cardiopulmonary function, improve their preoperative nutritional status, and prepare them for treatment. Regarding psychological aspects, patients were advised to pay atten-

tion to rest, avoid fatigue, listen to some light music, to not stay up late, and to engage in deep breathing and other emotional regulation activities before surgery.

After admission, members of the ERAS cohort underwent comprehensive assessment, such as preoperative nutritional assessment, liver function assessment, psychological screening, thrombosis risk assessment, pulmonary rehabilitation risk assessment, and mood thermometer assessment. Consultations were conducted by the nutrition, rehabilitation, respiratory, anesthesia, and pharmacy departments. One day before surgery, the anesthesiology department evaluated all patients for nausea and vomiting scores, basic diseases, and body mass index (BMI). Specialized nurses carried out cluster education, and nurses dedicated to individual education provided lung rehabilitation guidance.

Patients fasted for 6 hours before surgery, and drinking was prohibited 2 hours before surgery. Antibiotics were used in patients undergoing liver surgery, half an hour before the operation and more than 3 hours after surgery, to prevent infection. Attention was paid to keeping patients warm during the surgery; the operating room temperature was regulated at 22–24 °C, and a thermal insulation blanket, liquid heating, central temperature monitoring, and other technologies were used. Appropriate anesthesia, multi-mode analgesia, and preventive antiemetic drugs were also administered.

Postoperative multi-mode analgesia, including nonsteroidal analgesics and opioids, was implemented. Depending on the disease, target-oriented activity guidance and supervision of early activities, including turning over in bed, limb function activities, early out-of-bed activities, barometric therapy, and cardiopulmonary exercise, were provided. On the first day after surgery, multidisciplinary ward rounds were made; rehabilitation, nutrition, drugs, fluid rehydration, and other plans were formulated; and individualized treatment plans were set up and implemented among medical staff and patients. Specialist nurses revised the postoperative rehabilitation schedule of patients, provided guidance and feedback on the completion, and recorded all details.

Specialist nurses managed patients' psychological and rehabilitation programs. When the patient reached the discharge index, the doctor finalized the patient hospitalization records and prescriptions, and set the date of follow-up for the patient. Specialist nurses gave comprehensive education to patients on nutrition, activity, medicines, sleep, changing the incision dressing, and other matters requiring attention after discharge.

After discharge, patient information was extracted from the HIS, and a standardized postoperative follow-up was conducted and recorded. After discharge, the patients were followed up by telephone three times: 7, 14, and 30 days after surgery. Patients were consulted about the length of stay, and their diet, activity, pain, and sleep details were recorded.

Effect Evaluation

Data Collection

Clinical data were collected for each patient, and the nurse responsible created an electronic record of the case according to the actual situation of the patient's first clinical feeding, ability to get out of bed, flatulence, and defecation. The specialist nurses collected independent data for each patient and generated monthly statistics. One patient with brain injury after gallbladder surgery was excluded and withdrew from ERAS; after treatment, he recovered and was discharged home.

Evaluation Indicators

(1) The general data of patients undergoing hepatobiliary and pancreatic surgery included age, sex, education level, underlying diseases, and surgical methods.

(2) Postoperative risk assessment was conducted using the Nutrition Risk Screening 2002 (NRS2002) [11]. According to the NRS2002, nutritional status was determined using three variables: BMI, recent weight loss, and food intake 1 week before admission [12]. The NRS2002 score is the sum of the nutrition score, disease severity score, and age-adjusted score. The higher the score, the greater the risk of malnutrition. The Lung Rehabilitation Risk Screening Scale was developed according to the risk factors affecting pulmonary rehabilitation, including age >60 years, obesity (BMI >30.0 kg/m^2), history of smoking (>40 packs/year), and history of chronic cough or other respiratory diseases; the higher the assessment score, the higher the incidence of postoperative pulmonary complications. The most widely used individualized tool for monitoring and preventing the possibility of venous thromboembolism (VTE) occurring after surgery is the CAPRINI score [13]. The higher the score, the higher the likelihood of VTE. The mood thermometer score is used to accurately assess patients' mood changes; the higher the value, the greater the mood fluctuations. Postoperative nausea and vomiting (PONV) were evaluated using Apfel *et al*. 1999 [14]. Four risk factors for PONV were proposed: female sex, nonsmoking, postoperative opioid use, and history of motion sickness or PONV. The higher the Apfel score, the higher the incidence of postoperative nausea and vomiting.

(3) Postoperative recovery indicators included the time to first getting out of bed (hours), time to first oral ingestion (hours), time to first flatulence (hours), time to first defecation (hours), time to drainage tube removal (days) and length of hospital stay (days).

Statistical Methods

IBM SPSS Statistics 23 statistical software (IBM Corp, Armonk, NY, USA) was used for data analysis. The measurement data conforming to a normal distribution were expressed as the mean and standard deviation. Paired *T*-tests were used for age comparisons. The non-normal distribution measurement data were represented by the Median

Table 1. General data of patients in hepatobiliary and pancreatic surgery under ERAS (n = 226).

Variable	Classification	N	%
Sex	Male	109	48.3
	Female	117	51.7
Age	<40	23	10.18
	40–60	117	51.77
	>60	86	38.05
Education level	Below junior high school	110	48.6
	Junior high school and above	116	51.4
Site	Gallbladder	172	76.1
	Liver	43	19.0
	Biliary tract	11	4.9
Surgery type	Open	36	15.9
	Laparoscopic	190	84.1
Hypertension	No	164	72.5
	Yes	62	27.5
Diabetes	No	20	8.9
	Yes	209	91.1
Heart disease	No	7	3.1
	Yes	219	96.9
Lung disease	No	12	5.5
	Yes	214	94.5
Hepatitis B	No	27	12.0
	Yes	199	88.0

(min, max), and the Wilcoxon rank-sum test was used for comparisons between male and female groups. The count data were expressed as frequency and percentage, and the chi-squared test was used for comparisons between groups. p values < 0.05 were considered statistically significant.

Results

The general data of 226 patients in hepatobiliary and pancreatic surgery who met the inclusion criteria under the implementation of ERAS were analyzed. This group included both men (n = 109, 48.3%) and women (n = 117, 51.7%). The surgical methods were laparotomy (n = 36, 15.9%) and laparoscopy (190, 84.1%); the type of disease was gallbladder (n = 172, 76.1%), liver (43, 19.0%), or bile duct (n = 11, 4.9%) disease; and among the 226 patients, 27.5% had hypertension, 8.9% had diabetes, 3.1% had heart disease, 5.5% had lung disease, and 12.0% had hepatitis B (Table 1).

The study group was formed by performing 1:1 matching for age, chronic disease, and surgery type. Comparisons of the general data of inpatients undergoing hepatobiliary and pancreatic surgery showed no significant difference between male and female patients regarding age, education level, disease type, operation type, or underlying diseases (hypertension ($p = 0.180$), diabetes ($p = 0.673$), heart disease ($p = 1.000$), and lung disease ($p = 0.484$)). However, significant differences by sex were found for hepatitis B infection ($p < 0.001$), with significantly more male patients with hepatitis B than female patients (Table 2).

There was no significant difference between male and female patients undergoing hepatobiliary or pancreatic surgery with respect to postoperative nutritional risk screening assessment ($p = 0.233$), thrombosis risk assessment ($p = 0.881$), or mood thermometer score ($p = 0.927$). There were statistically significant differences regarding pulmonary rehabilitation risk ($p = 0.018$) and postoperative nausea and vomiting score ($p = 0.001$). Pulmonary rehabilitation risk in male patients (1(0,3)) was higher than that in female patients (0(0,2)). The postoperative nausea and vomiting score in female patients (2(1,3)) was higher than in male patients (1(0,2)) (Table 3).

There was no significant difference in the incidence of time to first oral ingestion ($p = 0.348$), time to first getting out of bed ($p = 0.125$), time to first flatulence ($p = 294$), time to drainage tube removal ($p = 0.122$), operation days ($p = 0.172$), postoperative hospital stay ($p = 0.692$), or total hospital stay ($p = 0.467$) between male and female inpatients undergoing hepatobiliary and pancreatic surgery ($p > 0.05$). There were significant differences in the time to first defecation ($p < 0.05$). Time of first defecation in male patients after surgery (36(10,78)) was longer than in females (31(4,61)) (Table 4).

Table 2. Comparison of general data between male and female inpatients undergoing hepatobiliary and pancreatic surgery.

Variable	Female (n = 49)		Male (n = 49)		χ^2	p
	N	%	N	%		
Education level					1.470	0.225
Below junior high school	28	57.14	22	44.90		
Junior high school and above	21	42.86	27	55.10		
Site					0.089	0.766
Gallbladder	43	87.76	42	85.71		
Other	6	12.24	7	14.29		
Surgery type					0.000	1.000
Open	3	6.12	3	6.12		
Laparoscopic	46	93.88	46	93.88		
Hypertension					1.800	0.180
No	32	65.31	38	77.55		
Yes	17	34.69	11	22.45		
Diabetes					0.178	0.673
No	45	91.84	47	95.92		
Yes	4	8.16	2	4.08		
Heart disease					0.000	1.000
No	46	93.88	47	95.92		
Yes	3	6.12	2	4.08		
Lung disease					0.489	0.484
No	46	93.88	43	87.76		
Yes	3	6.12	6	12.24		
Hepatitis B					12.391	<0.001
No	49	100.00	38	77.55		
Yes	0	0.00	11	22.45		
Chronic disease					0.000	1.000
No	24	48.98	24	48.98		
Yes	25	51.02	25	51.02		
	Mean	SD	Mean	SD	t	p
Age	56.90	10.66	56.90	10.66	0.000	1.000

Discussion

Clinical Implication

Over the past two decades, an increasing number of studies have been published investigating the safety and efficacy of ERAS programs in surgical patients, with many guidelines or consensus agreements across multiple surgical subspecialties [15]. ERAS includes three key indicators of recovery: promoting recovery of intestinal function, adequate analgesia, and early activity. However, there are few studies on sex differences among patients undergoing accelerated rehabilitation following surgery. In this study, we analyzed key measures for 226 patients undergoing accelerated rehabilitation following hepatobiliary and pancreatic surgery. We analyzed their general data, risk assessment, postoperative recovery indicators, and length of hospital stay. Temporal associations for incident gallstone disease and female sex, BMI, and non-HDL cholesterol, as well as inverse associations for increasing alcohol consumption and the cessation of hormone replacement therapy in female patients, were confirmed [16]. General data analysis showed there to be more males with hepatitis B infection than females. In postoperative risk assessment, there were differences in pulmonary rehabilitation risk and postoperative nausea and vomiting between male and female patients. Postoperative recovery indicators, including times to first defecation, were longer in male patients than in female patients.

Zettersten *et al*. [17] speculated that premenopausal women would have better outcomes after serious illness and injury owing to higher endogenous estrogen levels. The study by Nikfarjam *et al*. [18] revealed that male patients with acute cholecystitis were older and more likely to have gangrene cholecystitis than women, and had a risk of more comorbidities; men also had longer postoperative hospital stays than women. Rucker *et al*. [9] suggested that biologically higher levels of estrogen may reduce inflammation after trauma, and that less aggressive treatment and psychological interventions were more effective in women than in men. In developed countries, smoking is thought to be the most important cause of sex differences in life expectancy. Smoking is an important risk factor for malignant tumors (especially lung cancer) and cardiovascular and cerebrovas-

Table 3. Comparison of perioperative evaluation between male and female inpatients in hepatobiliary and pancreatic surgery.

Variable	Female (n = 49)	Male (n = 49)	Z	*p*
	Median (min, max)	Median (min, max)		
Nutritional risk screening	0(0,3)	0(0,4)	1.192	0.233
VTE risk assessment	4(0,9)	4(1,8)	1.490	0.881
Pulmonary rehabilitation risk	0(0,2)	1(0,3)	2.373	0.018
Mood thermometer	4(0,5)	3(1,5)	0.091	0.927
Postoperative nausea and vomiting	2(1,3)	1(0,2)	4.150	0.001

VTE, venous thromboembolism.

Table 4. Comparison of postoperative recovery indices between male and female inpatients in hepatobiliary and pancreatic surgery.

Variable	Female (n = 49)	Male (n = 49)	Z	*p*
	Median (min, max)	Median (min, max)		
Time to first oral ingestion (h)	6(6,19)	6(5,28)	0.393	0.348
First time out of bed (h)	7(4,23)	8(4,23)	1.535	0.125
Time to first flatulence (h)	12(4,36)	15(5,52)	1.050	0.294
Time to defecation (h)	31(4,61)	36(10,78)	2.620	0.009
Time to drainage tube removal (d)	0(0,5)	0(0,6)	1.545	0.122
Operation days (d)	1(0,11)	2(1,10)	1.365	0.172
Postoperative stay (d)	2(0,27)	2(1,11)	0.396	0.692
Length of hospitalization (d)	4(1,30)	5(2,15)	0.727	0.467

cular diseases [19]. Excessive alcohol consumption and poor blood pressure control among men also contribute to sex differences [20]. Our study showed that the lung rehabilitation risk in male patients was higher than that in female patients; this difference may have been due to the greater probability of smoking among men than women. Smoking could have contributed to the higher lung rehabilitation risk score in male than in female patients, which is one of the factors affecting prognosis.

Sex differences have been observed in many aspects of health care. Bechtel *et al*. [21] reported that women presenting for cardiac surgery tend to be older and more likely to have hypertension, diabetes, and high or low BMI than men. Women have increased risk of morbidity and mortality after many types of cardiac surgery, but lower mortality at mid- and long-term ranges. Choi *et al*. [22] reported, in terms of comorbidities, that more males died from diseases other than gastric cancer (GC), including other malignancies such as lung cancer, hepatocellular carcinoma, and pancreatic cancer, and respiratory diseases such as interstitial lung disease and chronic obstructive pulmonary disease; they also reported that more female patients died of cardiovascular or cerebrovascular deaths. Almasaudi *et al*. [23] reported that obesity prior to surgery for colorectal cancer increases the risk of infectious complications in both male and female patients. Increased BMI in male patients was associated with a greater risk of surgical site infections and wound infection than in female patients.

ERAS research must focus on investigation of the pathophysiological nature of the surgical traumatic stress response, in order to clarify the differences in pathogenesis of different postoperative complications and devise future strategies. In recent years, developments in this field have included precision hepatobiliary and pancreatic surgery, and continuous introduction of novel treatment concepts and methods, including minimally invasive surgery, 3D printing technology, and robotic surgery [24]. There are sex differences in perioperative recovery after hepatobiliary and pancreatic surgery, but using the ERAS method, these differences are minimized between male and female patients.

During the ERAS protocol, male patients that smoked were advised to quit smoking by professional physical therapists during the preoperative pulmonary rehabilitation risk assessment. The male patients were also given multimodal health education, preoperative postoperative aerobic training guidance, including deep breathing, abdominal movement, thoracic movement, effective cough, etc. Providing active pulmonary rehabilitation intervention during the perioperative period is one of the key aspects of ERAS [25]. After surgery, basic prevention, physical therapy and drug therapy were provided according to the defecation time and abdominal distension of male patients. For example, early postoperative ambulation, goal-oriented early activities, chewing gum, acupoint massage, and the use of laxatives were encouraged so as to promote intestinal peristalsis, defecation as soon as possible, reduce abdominal distension, and other conditions.

Limitations

As a single-center study, the prospective investigation of various diseases was lacking, and our study had a short research duration. The sample size was relatively small, most of the data collected were from gallbladder surgery, and there were few cases of liver, biliary, and pancreatic surgery. The collection of evaluation indicators for changes in psychological stress and compliance between male and female patients under ERAS is not complete. Unfortunately, we were not able to collect data regarding smoking in this dataset, and smoking is a major factor affecting lung rehabilitation and PONV score in both male and female patients. The perioperative pulmonary rehabilitation risk was higher in male hepatobiliary and pancreatic patients than their female counterparts, and the times to defecation were longer than those in women. In the future, the ERAS scheme for men may need to be different from that for women, targeting strengthening and promoting postoperative defecation, lung function exercises, and the provision of individualized health education to improve compliance among male patients and minimize the clinical differences between men and women.

Conclusion

In conclusion, we found a significant sex difference in postoperative recovery among patients receiving hepatobiliary and pancreatic surgery under implementation of the concept of accelerated rehabilitation surgery, with the recovery time of male patients being longer than that of female patients. It is important to reduce the differences in perioperative and postoperative recovery indicators of all patients, reduce the risk of pulmonary rehabilitation, and shorten postoperative defecation times. Moreover, sex differences in perioperative recovery indicators caused by obesity, drinking, and smoking should be addressed by future studies.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Author Contributions

XXZ and LGC conceived and designed this study. QW and MZ contributed to the study preparation, data collection, and data analysis and interpretation. DHP conducted data acquisition, and literature research and collection. LGC created the tables. XXZ was involved in writing and revising the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The protocols for the present study, which involves human participants, were reviewed and approved by the Ethical Committee of Taizhou Hospital of Zhejiang Province (number K20220129) on January 29, 2022, and the study was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments. Consent to participate was provided by each of the patients.

Acknowledgment

We thank the participants for their cooperation and support. We thank LetPub (https://www.letpub.com/) for its linguistic assistance during the preparation of this manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British Journal of Anaesthesia. 1997; 78: 606–617.

[2] Rollins KE, Lobo DN, Joshi GP. Enhanced recovery after surgery: Current status and future progress. Best Practice & Research. Clinical Anaesthesiology. 2021; 35: 479–489.

[3] Schwenk W. Enhanced recovery after surgery-Does the ERAS concept keep its promises. Der Chirurg; Zeitschrift Fur Alle Gebiete Der Operativen Medizen. 2021; 92: 405–420. (In German)

[4] Silveyra P, Fuentes N, Rodriguez Bauza DE. Sex and Gender Differences in Lung Disease. Advances in Experimental Medicine and Biology. 2021; 1304: 227–258.

[5] Bushnell CD, Chaturvedi S, Gage KR, Herson PS, Hurn PD, Jiménez MC, *et al*. Sex differences in stroke: Challenges and opportunities. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2018; 38: 2179–2191.

[6] Buxeda A, Redondo-Pachón D, Pérez-Sáez MJ, Crespo M, Pascual J. Sex differences in cancer risk and outcomes after kidney transplantation. Transplantation Reviews (Orlando, Fla.). 2021; 35: 100625.

[7] Patel DV, Yoo JS, Karmarkar SS, Lamoutte EH, Singh K. Sex Differences on Postoperative Pain and Disability Following Minimally Invasive Lumbar Discectomy. Clinical Spine Surgery. 2019; 32: E444–E448.

[8] Azap RA, Hyer JM, Diaz A, Tsilimigras DI, Mirdad RS, Pawlik TM. Sex-based differences in time to surgical care among pancreatic cancer patients: A national study of Medicare beneficiaries. Journal of Surgical Oncology. 2021; 123: 236–244.

[9] Rucker D, Warkentin LM, Huynh H, Khadaroo RG. Sex differences in the treatment and outcome of emergency general surgery. PloS One. 2019; 14: e0224278.
[10] van Dijk DPJ, van Woerden V, Cakir H, den Dulk M, Olde Damink SWM, Dejong CHC. ERAS: Improving outcome in the cachectic HPB patient. Journal of Surgical Oncology. 2017; 116: 617–622.
[11] Jia W, Liu W, Qiao X. Chinese Expert Consensus on Enhanced Recovery After Hepatectomy (Version 2017). Asian Journal of Surgery. 2019; 42: 11–18.
[12] Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clinical Nutrition (Edinburgh, Scotland). 2003; 22: 321–336.
[13] Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. Journal of Clinical Medicine. 2020; 9: 2467.
[14] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999; 91: 693–700.
[15] Zhang X, Yang J, Chen X, Du L, Li K, Zhou Y. Enhanced recovery after surgery on multiple clinical outcomes: Umbrella review of systematic reviews and meta-analyses. Medicine. 2020; 99: e20983.
[16] Shabanzadeh DM. New determinants for gallstone disease? Danish Medical Journal. 2018; 65: B5438.
[17] Zettersten E, Jäderling G, Bell M, Larsson E. Sex and gender aspects on intensive care. A cohort study. Journal of Critical Care. 2020; 55: 22–27.
[18] Nikfarjam M, Harnaen E, Tufail F, Muralidharan V, Fink MA, Starkey G, *et al*. Sex differences and outcomes of management of acute cholecystitis. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2013; 23: 61–65.
[19] Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, *et al*. Tobacco smoking and cancer: a meta-analysis. International Journal of Cancer. 2008; 122: 155–164.
[20] Yan R, Li W, Yin L, Wang Y, Bo J, PURE-China Investigators. Cardiovascular Diseases and Risk-Factor Burden in Urban and Rural Communities in High-, Middle-, and Low-Income Regions of China: A Large Community-Based Epidemiological Study. Journal of the American Heart Association. 2017; 6: e004445.
[21] Bechtel AJ, Huffmyer JL. Gender Differences in Postoperative Outcomes After Cardiac Surgery. Anesthesiology Clinics. 2020; 38: 403–415.
[22] Choi Y, Kim N, Kim KW, Jo HH, Park J, Yoon H, *et al*. Sex-based differences in histology, staging, and prognosis among 2983 gastric cancer surgery patients. World Journal of Gastroenterology. 2022; 28: 933–947.
[23] Almasaudi AS, McSorley ST, Horgan PG, McMillan DC, Edwards CA. The relationship between body mass index, sex, and postoperative outcomes in patients undergoing potentially curative surgery for colorectal cancer. Clinical Nutrition ESPEN. 2019; 30: 185–189.
[24] Lu SC. A brief analysis of hepatobiliary and pancreatic surgery in the era of precise medicine. Chinese Journal of Hepatobiliary Surgery. 2017; 23: 732–734.
[25] Zheng Y, Mao M, Ji M, Zheng Q, Liu L, Zhao Z, *et al*. Does a pulmonary rehabilitation based ERAS program (PREP) affect pulmonary complication incidence, pulmonary function and quality of life after lung cancer surgery? Study protocol for a multicenter randomized controlled trial. BMC Pulmonary Medicine. 2020; 20: 44.