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ABBREVIATIONS

EHETO Extrahepatic biliary tract obstruction

Surgical methods for biliary diversion include cholecystoduodenostomy and cholecystojejunostomy, but these procedures have been associated with high perioperative morbidity and mortality rates and short overall survival times in cats.1,4 In a recent study,1 for instance, perioperative complications, including refractory hypotension and hemorrhage, occurred in 80% of cats, and this high complication rate likely accounts for the fact that only 40% to 60% of cats described in previous reports1,4 survived long enough to be discharged from the hospital following biliary diversion surgery.

Causes for the high perioperative morbidity and mortality rates in cats undergoing biliary diversion surgery have not yet been identified. However, in previous reports1,4,11 involving 27 dogs that underwent biliary diversion surgery, 10 died within 6 weeks after surgery. Similarly, morbidity and mortality rates for human patients undergoing surgery for obstructive jaundice are reportedly high.1,3,12,13 The principal risk factors for death in human patients with obstructive jaundice undergoing surgery include a malignant cause for biliary obstruction, PCV < 30%, hypoalbuminemia, serum bilirubin concentration > 11 mg/dL, azotemia, and the presence of acute cholangitis.1,3,14 In patients with only 1 of these risk factors, the mortality rate is 9%, but in patients with ≥ 3 risk factors, it is 60%.13,14

Factors associated with a poor clinical outcome in cats with EHETO undergoing biliary diversion surgery have not been well characterized. The purpose of the study reported here, therefore, was to identify factors associated with outcome in cats with EHETO that undergo cholecystoenterostomy.

Criteria for Selection of Cases

Medical records of all cats examined at the Cummings School of Veterinary Medicine at Tufts University or the Angell Animal Medical Center between 1994 and 2003 were reviewed. Cases were eligible for inclusion in the study if EHETO had been confirmed surgically and a surgical biliary diversion procedure, such as cholecystoduodenostomy, cholecystojejunostomy, or choledochoduodenostomy, had been performed.

Procedures

Medical records for cases included in the study were reviewed, and a standardized data sheet was used.

In cats, EHETO may develop as a result of biliary neoplasia, pancreatic neoplasia, chronic pancreatitis, parasitic biliary infestation, or cholelithiasis.1,2 Because EHETO is uncommon in cats, guidelines for the medical and surgical management of affected cats have not been fully established. Nevertheless, it is clear that in cats with EHETO in which biliary tract patency cannot be reestablished, some form of biliary diversion procedure must be performed to allow decompression of the biliary tree.

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to collect information on signalment; history; initial complaint; clinical signs; physical examination findings; results of clinicopathologic testing, radiography, ultrasonography, and histologic evaluation of biopsy specimens; medical treatment; surgical treatment; anesthetic management; duration of hospitalization; discharge status; and long-term outcome. When necessary, owners and referring veterinarians were contacted for information on persistence or resolution of clinical signs, current medications, additional surgeries, survival time, and reason for death, if applicable.

Statistical analysis—Data are given as mean ± SD or median and range. Continuous data that were not normally distributed were logarithmically transformed prior to analysis. Independent *t* tests were used to compare mean values for continuous variables (eg, anesthetic time, age, and preoperative laboratory values) between cats that survived and cats that did not survive, and χ² tests were used to determine whether outcome (survived vs did not survive) was associated with categorical variables (eg, histologic diagnosis, sex, and treatment). For categorical values, independent *t* tests were used to compare mean survival times between categories. Pearson correlation analysis was used to determine whether survival time was correlated with continuous variables. All analyses were performed with standard software; values of *P* < 0.05 were considered significant.

Results

Twenty-two cases met the criteria for inclusion in the study. Cases included 16 cats examined at the Cummings School of Veterinary Medicine at Tufts University and 6 cats examined at the Angell Animal Medical Center. There were 15 domestic shorthairs, 4 domestic longhairs, 1 Burmese, 1 Maine Coon, and 1 Persian. Eleven cats were male (all spayed), and 11 were female (all spayed). Median age was 10 years (range, 3 to 17 years). The most common clinical signs were vomiting (n = 14), anorexia (13), lethargy and weakness (8), and weight loss (6). Physical examination abnormalities included icterus (n = 14), thin body condition (ie, body condition score < 4 on a scale from 1 to 9; 9), dehydration (7), signs of pain during palpation of the cranial portion of the abdomen (5), fever (rectal temperature > 39.2°C [102.5°F]; 4), thickened intestinal loops on palpation (4), obesity (ie, body condition score > 6; 4), abdominal distention (3), and palpable hepatomegaly (2). Eight cats were being treated for other diseases, including chronic vomiting (2), chronic inflammatory hepatic disease (2), idiopathic megacolon (1), lymphoplasmacytic interstitial nephritis (1), gastrointestinal tract lymphoma (in remission for 2 years; 1), and hypertrophic cardiomyopathy (1). One cat had undergone cholecystoduodenostomy 3 months earlier without resolution of clinical signs.

Median time from onset of clinical signs to initial examination was 24 days (range, 1 to 137 days). Nine cats had had clinical signs for < 8 days prior to examination, and 13 had had signs for > 20 days. All cats received some medical treatment prior to surgery. Five cats received medical treatment prior to referral, and 20 cats received medical treatment after referral but prior to surgery. Sixteen cats were given antimicrobials, 18 were given IV fluid therapy, and 5 were given prednisone because of lymphoma (n = 1) or presumptive or confirmed inflammatory hepatic or pancreatic disease (4). Sixteen of the 22 cats received parenteral vitamin K therapy, 7 received blood transfusions, and 4 received fresh frozen plasma prior to surgery.

A CBC was performed prior to surgery in 20 cats. Eight cats had nonregenerative anemia (PCV < 32%), with PCV at the time of admission ranging from 16% to 31%. The 7 cats that received a blood transfusion prior to surgery all had PCV < 20%. Eight cats had neutropenia with 1 cat having a left shift. Eleven cats had lymphopenia, and 2 cats had monocytosis.

Results of serum biochemical analyses performed prior to surgery were available for all 22 cats. The most consistent findings were high serum hepatic enzyme activities. Sixteen cats had high alkaline phosphatase activity (median, 355 U/L; range, 153 to 1,064 U/L), 19 had high alanine aminotransferase activity (median, 623 U/L; range, 324 to 2,719 U/L), and 22 had high aspartate aminotransferase activity (median, 129 U/L; range, 84 to 1,817 U/L). Thirteen of 16 cats in which γ-glutamyltranspeptidase activity was measured had high values (median, 16 U/L; range, 8 to 36 U/L). Twenty cats had high total bilirubin concentration (median, 6.86 mg/dL; range, 0.60 to 27.75 mg/dL). Eleven cats had high blood glucose concentration (median, 178 mg/dL; range, 123 to 248 mg/dL). Sixteen cats had hypercholesterolemia (median, 311 mg/dL; range, 237 to 474 mg/dL). Prothrombin time and activated partial thromboplastin time were evaluated in 10 cats. Prothrombin time was prolonged in 2 cats and partial thromboplastin time was prolonged in 4. Bilirubinuria was present in all 15 urine samples that were examined. Bacterial culture of urine samples from 3 cats failed to yield any growth.

Results of radiography performed prior to surgery were available for 12 of the 22 cats. Ten of the 12 cats had various nonspecific findings centered on the digestive system, and 2 cats did not have any abnormalities. Of the 10 cats with radiographic digestive system abnormalities, 3 had mild hepatomegaly, 1 had a focal opacity between the stomach and kidney and fluid-filled intestines, 1 had a focal area of reduced contrast caudal to the gastric silhouette, 1 had a suspected foreign body or right abdominal mass, 1 had a possible pancreatic mass, 1 had a local intestinal plication, 1 had functional ileus, and 1 had fluid and gas distension of the stomach. In 3 cats, thoracic radiography had been performed to check for evidence of metastatic disease; no thoracic abnormalities were seen in any of these cats.

Abdominal ultrasonography was performed in 21 of the 22 cats, and abnormalities suggestive of EHBTO were found in all 21. Abnormalities that were identified consisted of distension of the common bile duct (n = 15), distention of the gallbladder (8), an intra- or extraluminal mass obstructing the biliary tract (6), intrahepatic biliary duct distension (5), a visible biliary diverticulum (1), and a distend-
ed cystic duct (1). Other ultrasonographic abnormalities that were reported included hyperechoic hepatomegaly (n = 4), large pancreas (3), mild peritoneal effusion (3), small irregular kidneys (3), large duodenal papilla (2), large pancreatic duct (2), thick duodenum (2), gallbladder wall thickening (2), and hyperechoic pancreas (1).

Median time from admission to surgery was 2 days (range, 0 to 4 days), and median duration of hospitalization was 7 days (range, 2 to 11 days). Biliary diversion surgery was performed in all 22 cats and consisted of cholecystoduodenostomy (n = 13), cholecystojejunostomy (8), or choledochoduodenostomy (1). Surgery reports were available for 18 cats, and discharge instructions and daily physical examination findings were available for the remaining 4. Cholecystojejunostomy or cholecystoduodenostomy was performed on the basis of surgeon preference. Choledochoduodenostomy was performed in 1 cat because of the size of the common bile duct and proximity of the duodenum.

Anesthesia reports for 20 of the 22 cats were reviewed. Blood pressure was monitored in 15 cats by means of Doppler ultrasonic flow detection. Eleven of these 15 cats had episodes of intraoperative hypotension (ie, systolic blood pressure < 80 mm Hg), with 9 cats having hypotension severe enough to warrant intervention. Most episodes of hypotension occurred after more than 45 minutes of anesthesia and persisted for the remainder of the surgical procedure. Several strategies were attempted to correct the hypotension including fluid administration for volume replacement, administration of vasopressors, and use of alternative anesthetic strategies to decrease use of systemic anesthetics. Interventions consisted of administration of 1 or more units of packed RBCs (n = 8), administration of 1 or more boluses of 6% hetastarch (7), administration of fresh frozen plasma (5), administration of a continuous rate infusion of dopamine (4), administration of a continuous rate infusion of fentanyl (1), epidural administration of morphine sulfate (1), and epidural administration of bupivacaine (1). Other anesthetic management techniques used because of complications included ventilatory support (n = 3), administration of anticholinergics for bradycardia (3), and IV administration of calcium for hypocalcemia secondary to administration of blood products (1).

Following surgery, fluids were administered IV and opioid pain medications and antimicrobials were administered parenterally in all cats. Postoperative complications were common and included vomiting, anemia, hypotension, and anorexia. Anemia was documented in all 18 cats in which PCV was measured after surgery (median PCV, 20%; range, 18% to 27%) and was treated with transfusions of packed RBCs (n = 15) or administration of hemoglobin glutamer (1). Suspected coagulopathy was treated with parenteral vitamin K administration in 5 cats and fresh frozen plasma in 4 cats. Persistent postoperative hypotension (systolic blood pressure < 80 mm Hg) was treated with blood products in 14 cats and colloids in 9 cats. Three cats required a continuous rate infusion of metoclopramide to control vomiting. Three cats with persistent anorexia and vomiting received parenteral nutrition.

Results of serum biochemical tests performed between 1 and 14 days after surgery were available for 16 cats. Cats in which follow-up serum biochemical testing was not performed died (n = 3), were quickly discharged because of a rapid clinical response to surgery (2), or were euthanized (1). In all 16 cats in which serum biochemical testing was performed after surgery, serum was reported to be icteric. Hyperbilirubinemia was present in 11 cats, and hypoproteinemia was present in 8. Serum alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase activities were still high in 12, 7, and 11 cats, respectively, although postoperative values were lower than preoperative values in all 16 cats. Serum bilirubin concentration was high in 13 cats, and serum cholesterol concentration was high in 4. In 14 cats, postoperative total bilirubin concentration was lower than the preoperative values. In the other 2, total bilirubin concentration was not reported (n = 1) or was increased, compared with the preoperative value (1).

Samples of liver (n = 20), gallbladder (12), pancreas (9), lymph nodes (7 mesenteric and 1 pancreatic), duodenum (7), common bile duct (7), jejunum (6), kidney (1), stomach (1), and omentum (1) were submitted for histologic examination. In 9 cats, the obstructing lesion was neoplastic, with histologic diagnoses including biliary adenocarcinoma (n = 5), lymphoma (2), squamous cell carcinoma of the duodenum and pancreas (1), and exocrine pancreatic carcinoma (1). Intra-abdominal metastatic disease was confirmed in cats with squamous cell carcinoma (1), exocrine pancreatic carcinoma (1), and biliary adenocarcinoma (1). The pancreatic carcinoma was correctly identified by means of cytologic examination of an ultrasound-guided fine needle aspirate prior to surgery. Five of the 9 cats with neoplasia had concurrent chronic inflammatory hepatobiliary disease.

In 13 cats, chronic inflammatory disease was identified as the cause of EHBTO. Chronic hepatitis (n = 10), cholecystitis (8), pancreatitis (7), and enteritis (5) were documented histologically, and in 10 of the 13 cats with chronic inflammatory disease, 2 or more of these areas were involved. Five of the 13 cats with chronic inflammatory disease had a fibrotic bile duct mass identified as the cause of EHBTO.

Samples from 10 and 16 cats, respectively, were collected at the time of surgery and submitted for anaerobic and aerobie bacterial culture. Samples submitted for bacterial culture were collected from the gallbladder (n = 10), bile (7), liver (6), bile duct (1), abdominal fluid (1), and pancreas (1). For all 10 samples, anaerobic bacterial culture failed to yield any growth. Aerobic bacterial culture of 3 bile samples yielded bacterial growth; organisms that were identified included Staphylococcus intermedius (1), Escherichia coli and Pseudomonas aeruginosa (1), and Entero bacter faecalis and Enterococcus cloacae (1). Aerobic bacterial culture of 2 liver samples yielded growth; organisms that were identified included Enterococcus spp (1) and E coli (1). Aerobic culture of 1 gallbladder sample yielded E coli. Five cats with positive bacterial culture results had inflammatory disease, and 1 had lymphoma.
Median survival time for the 13 cats in which chronic inflammatory disease was identified as the cause of EHBTO (255 days; range, 4 to 2,196 days) was significantly \( (P = 0.04) \) longer than median survival time for the 9 cats in which neoplasia was identified as the cause of EHBTO (14 days; range, 0 to 115 days). Nine of the 13 cats with chronic inflammatory disease and 5 of the 9 cats with neoplasia survived long enough to be discharged from the hospital; these proportions were not significantly different. One cat with squamous cell carcinoma had cardiac arrest and died immediately after surgery, and 3 cats with biliary adenocarcinoma were euthanized because of development of septic peritonitis \( (n = 2) \) or the poor long-term prognosis \( (1) \). One cat with chronic inflammatory disease died 2 days after surgery because of severe hepatic encephalopathy and hepatic failure, and 1 died 8 days after surgery because of cardiopulmonary arrest. One cat with chronic inflammatory disease was euthanized 12 days after surgery because of recurrent fever, and 1 was euthanized 13 days after surgery because of vomiting.

Three of the 14 cats that were discharged from the hospital were lost to follow-up. Median survival time for the 6 cats with chronic inflammatory disease that were discharged from the hospital \( (447 \text{ days}; \text{range, } 240 \text{ to } 2,196 \text{ days}) \) was significantly \( (P = 0.006) \) longer than median survival time for the 5 cats with neoplasia that were discharged \( (31 \text{ days}; \text{range, } 14 \text{ to } 115 \text{ days}) \). Only 6 cats survived >6 months after surgery, and all of these cats had chronic inflammatory disease. Complications in the cats that survived >6 months after surgery included recurrent cholecystitis \( (n = 3) \), intermittent vomiting \( (2) \), and diarrhea secondary to exocrine pancreatic insufficiency \( (1) \). Three cats received antimicrobials long-term; 2 were fed a low-fat, easily digestible diet\(^4\); and 1 received pancreatic enzyme replacement.\(^4\) Causes of death for 5 of the 6 cats that survived >6 months after surgery were hepatic failure \( (n = 3) \), acute anemia \( (1) \), and mandibular cancer \( (1) \). The remaining cat was still alive 990 days after surgery.

Other than underlying cause \( (\text{ie, chronic inflammatory disease vs neoplasia}) \), none of the historical or clinical signs, clinicopathologic results, anesthetic complications, or surgical treatments were significantly associated with outcome.

Discussion

Results of the present study suggest that in cats undergoing cholecystoenterostomy because of EHBTO, the underlying cause of the obstruction was significantly associated with outcome. Specifically, cats in which EHBTO was a result of neoplasia had a significantly shorter median survival time than did cats in which EHBTO was a result of a chronic inflammatory disease. However, underlying cause was not significantly associated with survival to discharge, in that 5 of the 9 cats with neoplasia and 9 of the 13 cats with chronic inflammatory disease survived long enough to be discharged from the hospital.

Median survival time for cats with chronic inflammatory disease that were discharged from the hospital was 447 days, whereas median survival time for cats with neoplasia that were discharged from the hospital was only 31 days. This difference may reflect the fact that in 5 of the 9 cats in the present study, the tumor causing EHBTO was a biliary adenocarcinoma or exocrine pancreatic carcinoma. Both of these are locally aggressive tumors that typically metastasize early in the course of the disease,\(^5,7\) and effective chemotherapy protocols for these tumors have not been developed.

Chronic inflammatory disease involving the liver, gallbladder, pancreas, or intestines was the cause of EHBTO in 13 of the 22 cats in the present study, with 10 of the 13 cats having involvement of >1 organ. Inflammatory disease involving a triad of abdominal organs has been described in cats,\(^1,8,20\) and although the pathogenesis of this inflammatory disorder is unknown, there is evidence that immune dysregulation or chronic infectious disease may play a role.\(^1,3,22\) Given that this inflammatory disease process is progressive, affected cats can be expected to eventually develop signs of hepatobiliary, pancreatic, or intestinal failure. Thus, simply restoring bile flow in cats with this chronic progressive inflammatory disorder is unlikely to reverse the pathologic process. Many cats in the present study continued to have signs of gastrointestinal tract or hepatobiliary disease \( (\text{eg, chronic intermittent vomiting or exocrine pancreatic insufficiency}) \) after surgery or died as a result of hepatic failure.

Although cholelithiasis has previously been reported to be a potential cause of EHBTO in cats,\(^2\), none of the cats in the present study were found to have cholelithiasis. Three studies\(^4,5,7\) have reported on clinical outcome after biliary diversion surgery in cats with cholelithiasis. In these studies, 75% of cats survived to discharge, and cats that were discharged lived, on average, 2 years after surgery, often dying of unrelated disease. The apparently better clinical outcome in cats with cholelithiasis, compared with cats in the present study, may be related to the fact that in cats with cholelithiasis, hepatobiliary function can be expected to return to normal once the choleliths have been removed and any accompanying bacterial infection has been treated appropriately.

In our study, information on only 27 dogs with EHBTO that underwent cholecystoenterostomy has been reported in the veterinary literature.\(^1,3,8,12\) An underlying cause was reported for 16 of those dogs, of which 12 had chronic pancreatitis, 2 had neoplasia (duodenal gastrinoma and pancreatic adenocarcinoma), 1 had a pseudocyst, and 1 had cholelithiasis. Both dogs with cancer died shortly after surgery, whereas 9 of the 12 dogs with chronic pancreatitis survived following surgery, with survival time ranging from 8 to 48 months. Thus, although additional studies are needed, it appears that, as was the case for cats in the present study, the prognosis for dogs with EHBTO secondary to inflammatory disease is better than the prognosis for dogs with EHBTO secondary to neoplasia.

Cats with EHBTO are considered to have a high risk for anesthetic and surgical complications. Intraoperative hypotension was identified in 11 of 15 cats in the present study and has been documented in previous reports.\(^1,7\) A similar phenomenon is seen in human patients with obstructive jaundice.\(^1,21\) The pathophysiol-
ogy of this refractory hypotension is incompletely understood, but studies of cats, dogs, and rodents with experimentally induced obstructive jaundice suggest that decreased vascular responsiveness to vasoressors and decreased myocardial contractility play a role. Poor vascular responsiveness in patients with obstructive jaundice may be a result of systemic endotoxia or increased production of the vasodilatory compound nitric oxide or may be secondary to vagal effects associated with manipulation of the biliary tract. Endotoxia is linked to bacterial translocation of gram-negative bacteria from the gut secondary to the absence of intraluminal bile acids, decreased gut barrier function, and impaired clearance of endotoxin by Kupffer cells. Studies involving human patients in which therapeutic interventions, such as oral administration of bile acids or lactulose and parenteral nutrition, were used to decrease circulating concentrations of endotoxin or cytokines have shown that such procedures have limited success in improving surgical outcome in patients with biliary obstruction. However, these strategies have not been examined in cats with obstructive jaundice.

Anemia severe enough to necessitate blood transfusions was a common complication in the present study. The etiology of this progressive anemia was multifactorial. Many cats had normocytic, normochromic, nonregenerative anemia prior to surgery, likely because of chronic disease, and blood loss during surgery exacerbated this condition. Dissection of the gallbladder from the hepatic fossa can result in substantial blood loss because the liver parenchyma is highly vascular. Because longstanding EHBTO can result in malabsorption of fat and secondary vitamin K deficiency, cats may also have had subclinical coagulopathy, which would have contributed to the blood loss during surgery. Other factors that may have contributed to the anemia among cats in the present study include administration of large volumes of fluids leading to a dilutional coagulopathy and gastrointestinal tract hemorrhage. Given our findings, we suggest that blood products be on hand before attempting biliary diversion surgery. This recommendation is preoperative and postoperative bacterial infections.

Aerobic bacterial growth was obtained from 6 of 16 sample collection. On the other hand, postoperative infection appeared to be uncommon, in that only 2 of the 22 cats had clinical evidence of postoperative infection. Recurrent biliary tract infection secondary to enterobiliary reflux has been reported as a potential long-term complication of biliary diversion surgery in cats, but determining the incidence of recurrent biliary tract infection in the present study was hampered by less than optimal long-term follow-up.

Because cats undergoing surgery for EHBTO have a high risk of developing anesthetic and surgical complications, techniques to provide temporary biliary decompression that allow time for patient stabilization and partial return of hepatic function could have a positive impact on clinical outcome. In a study in people, preoperative transhepatic biliary drainage or biliary decompression via endoscopic stent placement was not shown to improve overall surgical morbidity or mortality rate. However, there is a subpopulation of human patients that benefit from preoperative biliary drainage, including those with acute cholangitis, coagulation problems, or malnutrition. In a study of cats with experimentally induced EHBTO, temporary biliary drainage effectively reversed the increases in serum bilirubin concentration and hepatic enzyme activities and resolved clinical signs attributable to EHBTO. The use of temporary biliary decompression in cats with EHBTO warrants further investigation.

The median time from onset of clinical signs to initial examination for cats in the present study was 24 days. Because chronic biliary obstruction can itself result in irreversible inflammatory and fibrotic changes, mos timely diagnosis of EHBTO might improve the clinical outcome in affected cats. Clinical signs, physical examination findings, and serum biochemical abnormalities in cats with EHBTO are nonspecific, and although abdominal radiography can detect approximately 50% of choleliths, other radiographic abnormalities in cats with EHBTO are nonspecific. Currently, ultrasonography is the best and most cost-effective method for evaluating the biliary system in cats and dogs and has been reported to have up to 85% accuracy for diagnosis of EHBTO in cats. In the present study, abnormalities suggestive of EHBTO were found in all 21 cats that underwent ultrasonography. Ultrasonography is useful for assessing not only the liver but also surrounding organs, which is important given the high proportion of cats with pancreatic and intestinal inflammation in the present study. In cats with icterus, ultrasonography should be performed early in the course of management, but serial ultrasonography may be required, as definitive signs of EHBTO may take time to become evident. Other diagnostic imaging modalities, such as computed tomography and scintigraphy, could be useful in assessing patients suspected to have EHBTO, but both require anesthesia. Additional studies are needed to determine the sensitivity and specificity of these imaging modalities in the diagnosis of EHBTO in cats.

There were a number of limitations to the present study. In particular, the sample size may have been too small to identify significant prognostic indicators or risk factors, and the loss of cats to follow-up further decreased the statistical power. Various surgeons with variable experience performed cholecystoenterostomies, which may have introduced bias. Finally, because of its retrospective nature, the study could not accurately assess the impact of any intraoperative or postoperative interventions on clinical outcome.

In conclusion, results of the present study suggest that cats with EHBTO secondary to neoplasia have a poorer prognosis than cats with EHBTO secondary to chronic inflammatory disease. However, the overall prognosis for cats with EHBTO undergoing cholecystoenterostomy must be considered guarded to poor, and

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1380 Scientific Reports: Retrospective Study

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the incidence of perioperative complications, including refractory hypotension, anemia, and infection, is high. Future studies are needed to devise methods to allow for earlier diagnosis and improve treatment.


