

**Anne Burnett Marion School of Medicine at
Texas Christian University**

**Malnutrition and Surgical Outcomes:
Making a Connection for Patients in Total
Pancreatectomy with Islet
Autotransplantation**

Caden Duffy
MD Candidate, Class of 2024

ABSTRACT

RESEARCH QUESTION

How does presurgical nutritional status for patients undergoing total pancreatectomy with autoislet transplantation correlate with intraoperative and postoperative complications?

BACKGROUND

For patients suffering severe pain refractory to medical management due to chronic pancreatitis, a possible therapeutic approach is a total pancreatectomy. As a result of this surgery, many patients suffer from brittle diabetes due to the removal of the islets of Langerhans, which contain the endocrine cells that function to control glycemic levels. Surgical intervention of either autologous or allogenic islet transplantation, using either the patient's own pancreatic islets or donor islets, can restore secretion of pancreatic hormones necessary for energy regulation.

Patient nutritional status has been shown to have a significant impact on postsurgical outcomes for a variety of surgeries. However, it has not been extensively studied in patients undergoing pancreatic islet transplantation following total pancreatectomy. The focus of this retrospective study is to look at patients who have undergone total pancreatectomy with autoislet transplantation to control pain for chronic pancreatitis and compare the postoperative outcomes of patients who are undernourished, compared to well-nourished, and look for correlations between these two groups. This research will help surgeons have improved predictive power for achieving positive surgical outcomes which might be used to better screen and prepare patients for surgery.

METHODS

Data for this study was collected through REDCap, Microsoft Excel, and the electronic medical record Epic. Measures of the patients' nutritional status such as their subjective global assessments and presurgical BMIs were also obtained. Intraoperative complications and blood loss were recorded. Postoperative variables that were recorded include length of hospital and ICU stays, surgical complications, and feeding tube duration. Data was compiled and analyzed using Microsoft Excel and GraphPad Prism.

RESULTS

The anticipated result was that poor nutritional status prior to TPIAT surgery would be correlated with an increased likelihood of complications. Despite our smaller data set of patients who underwent nutritional evaluation accessible through Epic, there was a trend for patients who were moderately nourished to have fewer postsurgical complications (36%) compared with those that were well-nourished (54%), although due to our small sample size the difference was not statistically significant. Despite this lower percentage, a relatively higher percentage of moderately nourished patients had more severe complications of a Clavien-Dindo classification III or above than those that were well nourished (66% of total complications compared to 14%). Length of total hospital stay was not statistically different between moderately nourished (13 days) and well-nourished (15 days, p-value: 0.63). Length of stay in intensive care was also similar between moderately nourished (1.9 days) and well-nourished (1.5 days, p-value: 0.36).

CONCLUSION

Nutritional status of patients has been shown to be an important prognostic indicator to help evaluate patients for surgery. In TPIAT, more patient data is needed to confidently discern a correlation between presurgical nutrition and surgical complications. However, patients who are undernourished appear to experience more severe complications than their well-nourished counterparts. Despite this observation, there does not appear to have differing hospital lengths of stay or any difference in time spent requiring critical care that correlates with presurgical nutritional status.

RESEARCH QUESTION

The research question of this retrospective study is: How does nutritional status for patients undergoing total pancreatectomy to control pain for chronic pancreatitis correlate with surgical outcomes? For the purpose of this study, patients will be divided into two cohorts: those who were categorically defined as moderately undernourished and patients who are well-nourished prior to surgery. A comparison of adverse surgical events and postsurgical outcomes of these two patient groups will then be made. The anticipated outcome is that those who are malnourished prior to undergoing total pancreatectomy with islet autotransplantation will have more adverse surgical events and overall poorer postsurgical outcomes.

INTRODUCTION AND SIGNIFICANCE

Chronic pancreatitis (CP) is characterized by irreversible damage to the structure and function of the pancreatic parenchyma. Having an incidence of 40-50 per 100,000 people in the United States, CP most commonly affects middle-aged males.¹ Alcohol consumption is a well-recognized risk factor that increases susceptibility to CP, but several other contributing factors include autoimmune disease, genetic disorders such as cystic fibrosis, gallstones, endoscopic retrograde cholangiopancreatography, and other idiopathic causes.² Genetic evaluation is often considered and performed with patients undergoing surgical evaluation, with known mutations *PRSSI* and *SPINK1*, in addition to *CFTR*, being correlated with CP. In general, severe abdominal pain is what motivates patients to seek treatment for CP.³ Early interventions which are considered include pain management through analgesia and nerve blocks, and surgical interventions such as endoscopic decompression, surgical decompression of the main pancreatic duct, and partial pancreatic resection.⁴

When surgical and pain management options are deemed insufficient to control pain due to CP, patients are referred for total pancreatectomy. These patients may undergo initial treatment with a partial pancreatic resection, typically involving the removal of the pancreatic tail, prior to consideration for total pancreatectomy. This is due to a total pancreatectomy resulting in a more extensive operation with manipulation of the biliary duct system. An additional adverse consequence of removing the entire pancreas is the complete loss of pancreatic exocrine function and the removal of the pancreatic endocrine cells which regulate glycemic levels. While enzyme supplementation can restore the digestive exocrine function in patients undergoing TP, the wide swings from hypoglycemia to hyperglycemia due to insufficient endocrine compensatory mechanisms results in a brittle diabetic state, which

increases both morbidity and mortality.⁵ Despite these risks, a total pancreatectomy (TP) has proven efficacy at reducing pain which patients often find intolerable.⁶ Total pancreatectomy with islet autotransplantation (TPIAT), where a patient's own pancreatic islets are isolated from their removed pancreas, which is then transplanted back into the portal vein, is a promising strategy that may be used to preserve pancreatic endocrine function and reduce some of the morbidity associated with TP.⁷

Postsurgical complications are common in any major abdominal surgical procedure, including TPIAT. In TP alone, morbidity ranges from 15 – 65%, with the most commonly reported complications in the literature including bleeding and sepsis.⁸ Although the risk of complications with these procedures is high, few studies have looked at preoperative factors which lessen postsurgical complications in TPIAT. Malnutrition has been shown to negatively impact postsurgical outcomes in a variety of fields, with recent studies showing its impact from hepatectomy⁹ and cleft lip and palate surgery¹⁰ to colorectal¹¹ and orthopedic trauma surgery.¹² With regard to TPIAT, there is no well-established universal standard for screening the nutritional status of patients with CP, and it is often an overlooked variable despite the effect it could play in postsurgical complications.¹³ Determining a standard method for assessing nutritional status will help to allow for optimization of patient prehabilitation prior to surgery so that the process might go as smoothly as possible.

This study is aimed at establishing a precedence for screening patients with CP for nutritional status prior to undergoing TPIAT. The significance of this research is to increase awareness regarding the standards by which patients undergoing TPIAT may be screened for nutrition and using that data to determine if it is an indicator for how well a patient might do postoperatively. Early nutritional intervention may be quickly initiated and modified, with the

possibility of making patients better surgical candidates. This can be performed by optimizing oral intake or using interventions like nasogastric tubes or percutaneous endoscopic gastrostomy feeding tubes to deliver the required nutrition more directly. Undernutrition is a variable which can also be directly modified prior to surgery using oral nutritional supplementation,¹⁴ allowing for a less invasive method to be considered in improving the nutrition of surgical patients. This enhanced preoperative preparation may also lead to cost savings and decrease adverse postoperative events for this subset of patients.

RESEARCH MATERIALS AND METHODS

A dataset used in a recent publication from Drs. Bashoo Naziruddin and Nicholas Onaca were used as a framework for the methods.¹⁵ Retrospective data from patients who have undergone TPIAT at Baylor University Medical Center in Dallas, Texas within the last 10 years was examined. These patients had a multidisciplinary team of physicians diagnose them with chronic pancreatitis, which included a transplant surgeon, endocrinologist, and gastroenterologist. Their symptoms included severe pain which was refractory to other pain management techniques.

Patient data before and after surgery was obtained, which included age, sex, date of surgery, history of a previous pancreas operation, diagnosed duration of chronic pancreatitis, cause of pancreatitis if known, whether the patient had preexisting diabetes, hospital length of stay, and ICU length of stay. Adverse effects were measured, which were reported using the Common Terminology Criteria for Adverse Effects in Trials of Adult Pancreatic Islet Transplantation (version 4.1, May 2008). Surgical complications were recorded and graded using the Clavien-Dindo classification.¹⁶ We defined any complication during the perisurgical or postsurgical period of a classification II or above as a surgical complication and differing from the expected clinical course. Patients were followed for a minimum of three months postoperatively to monitor for complications.

Nutritional evaluation was completed using a standardized method of subjective global assessment. This method has been validated in use with other abdominal transplantation procedures, including liver, and more details are described in the following citation.¹⁷ Additional indicators for nutritional status were also obtained, including the length of tube feeding both prior to the surgery and after and presurgical BMI. Since tube placement can vary based on the

route that feeds are administered, and given the prevalence of nasogastric tubes in these transplant patients, we followed patients for three months postoperatively to identify if they still were using iatrogenic means to receive nutrition.

Statistics

Tests of significance included two-tailed unpaired Student t test and Fisher's exact test as appropriate. Due to the low sample size, we elected to use Fisher's exact test over Chi-squared analysis. We used an unpaired design that did not assume Gaussian distribution and used nonparametric testing. Welch's t test was used to correct for any difference in standard deviation. P-values will be considered significant when less than 0.05. GraphPad Prism 10 (Version 10.1.1) was used for statistical analysis and creating the figures below.

Sample size

Baylor Scott and White has performed over 200 TPIAT procedures over the last several years. In spite of the number of surgeries being relatively low, the patients who undergo TPIAT are well charted and followed. The recent publication referenced above had 108 patients included as part of the study. This included a 48% incidence of postoperative complication on first admission. To achieve a power of 0.8, with $\alpha = 0.05$, anticipating a 50% increase in incidence of postoperative complication on first admission for undernourished patients, and an enrollment ratio of 3 well-nourished patients to 1 undernourished patient in the study, I anticipated needing a sample size of 174 patients to show significance. Unfortunately, data from Epic was only able to obtain nutritional information on patients that had received TPIAT from September 2019 until

the present. This data was obtained and resulted in 27 patients that had results of full nutritional evaluation and charted surgical courses.

Software

Patient data has been collected using REDCap, Microsoft Excel, and the electronic medical record Epic. The analysis of accessed patient data was performed in Microsoft Excel and GraphPad Prism.

RESULTS

From our initial data set, we obtained the information of 212 patients which have undergone TPIAT between 2007 and 2021 at Baylor University Medical Center. From this set, we excluded 61 patients due to limited data that were missing information on recorded complications during the surgical and postsurgical periods. These patients primarily had their surgeries from 2008 until 2018 and we had limited access to their medical records which were stored in a separate electronic medical record system.

To further characterize the 151 patients in our sample, 51 were male and 100 were female. The average age at time of surgery was 39, ranging from the ages of 13 to 65. A total of 11 patients had received an operation involving the pancreas prior to TPIAT. These previous surgeries included a Whipple operation, a distal pancreatectomy, a Peustow procedure and a pancreatojejunostomy.

Nutritional assessments were obtained on the most recent 27 patients. Of this subset of patients, 9 of them had preoperative nutritional intervention of either a PEG tube or a jejunostomy tube. Only 5 out of the 27 patients were using similar interventions at three months postoperatively. Of note, only 4 patients of the 27 had no documentation of requiring any form of supplemental nutrition administration. Most patients required at least a temporary nasogastric tube for medication and nutrition administration.

Surgical complications that were recorded from the set of 151 patients included incidence of delayed gastric emptying (17%), surgical site infection (11%), postoperative pneumonia (7%), thrombosis (6%), urinary tract infection (5%), small bowel obstruction (4%), organ space infection (4%), gastric perforation (4%), urinary retention (3%), cardiovascular complication (3%), PICC line infection (2%), and septic shock (1%). The smaller subset of data only including

the 27 patients with full nutritional assessments had similar incidence and is compared to the larger data set in Table 1.

	Full Data (%)	Nutrition Subset (%)
Delayed Gastric Emptying	25 (17%)	5 (19%)
Surgical Site Infection	16 (11%)	3 (11%)
Postoperative Pneumonia	11 (7%)	2 (7%)
Thrombosis	9 (6%)	1 (4%)
Urinary Tract Infection	8 (5%)	1 (4%)
Small Bowel Obstruction	6 (4%)	0 (0%)
Organ Space Infection	6 (4%)	1 (4%)
Gastric Perforation	6 (4%)	0 (0%)
Urinary Retention	5 (3%)	1 (4%)
Cardiovascular Complication	4 (3%)	0 (0%)
PICC Line Infection	3 (2%)	1 (4%)
Septic Shock	1 (1%)	0 (0%)

Table 1: Recorded surgical and postsurgical complications following TPIAT after 3 months.

Subjective global assessment results were obtained on the nutritional subset of 27 patients, classifying patients into well-nourished (13 patients) or moderately nourished (14 patients). These patients were analyzed further based on the variables described above.

Surprisingly, there was a trend for patients who were moderately nourished to have fewer postsurgical complications (36%) compared with those that were well-nourished (54%) although this difference was not statistically significant due to the small sample size (p-value: 0.45). Despite this lower percentage, a relatively high percentage of moderately nourished patients (66%) had more severe complications of a Clavien-Dindo classification III or above than the relative percentage of those that were well nourished (14%). Length of total hospital stay was not statistically different between moderately nourished (13 days) and well-nourished (15 days, p-value: 0.63). Length of stay in intensive care was also similar between moderately nourished (1.9 days) and well-nourished (1.5 days, p-value: 0.36). For graphical representation of these trends, see Figure 1.

a)

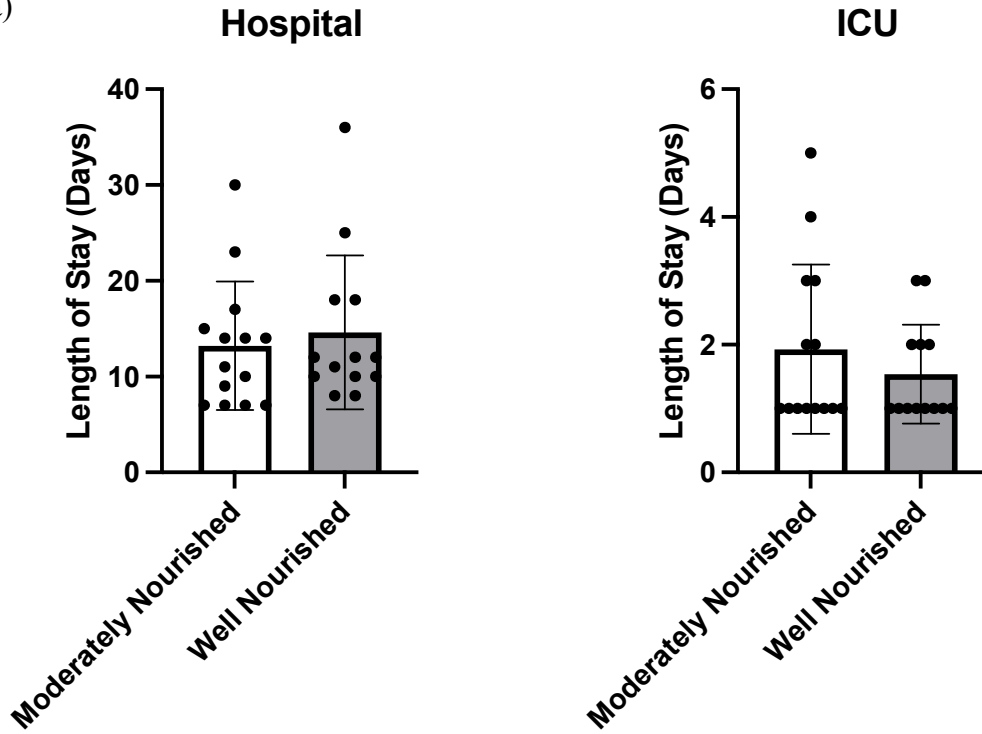


Figure 1: Comparison of length of stay (a) at hospital and (b) in intensive care (Mean \pm SEM).

DISCUSSION AND INNOVATION

As can be seen in the results above, there does not seem to be a higher number of total surgical complications in moderately nourished patients. However, the surgical complications for these undernourished patients seems to be more severe in a higher relative percentage of patients. Although this does not correlate with an increase in the average number of days in the hospital or intensive care unit, there was a larger range of days that moderately nourished patients were staying in the ICU. A confounding factor is how medically complex many of these patients are and the various comorbidities that contribute to prolonged hospital stays. This variability might be decreased if nutritional assessment data was obtained on an increased number of patients.

The complication types and rates observed in this study are similar to those that have been reported in the literature as described above. This high rate of morbidity is expected with an invasive procedure like TPIAT. The most common complications from our data included decreased gastric emptying, surgical site infection, and postoperative pneumonia. Fortunately, these complications are routinely encountered after an operation and can be corrected medically. Of note, none of these three common complications directly involved sepsis or bleeding, but incidence of these complications did occur albeit less frequently.

While medical and scientific advances have drastically improved healthcare outcomes, few advances have had as large of an impact as improving nutrition. For patients undergoing TPIAT who can often not tolerate oral intake due to pain, this improvement of nutrition comes through finding alternate routes for administration to deliver food and medications. As we saw from our data, gastric and jejunostomy tubes for long term support, or nasogastric tubes for short term treatment, were used in most patients. The length of supplemental feedings was similar among patients that were both moderately nourished and well-nourished likely due to the

necessity for access during their hospital stays. Many patients have difficulty tolerating food after an operation, and diets must be slowly advanced as tolerated to avoid retching. The act of vomiting can also put pressure on sutures and staples used during the operation, so antiemetics and tube feedings are often employed perioperatively to minimize this possibility.

TPIAT is a procedure which is still being actively developed. Any improvements to the surgical outcomes specifically for this procedure will help to make it a more reliable treatment option for patients with CP. Although this data benefits from having many years from which to analyze patients, the surgical procedure and operative steps for TPIAT are being continually improved and may have a large impact on surgical outcomes. Although no difference was noted in surgical complications or in the types of candidates that were undergoing the surgery from our data set, that is a factor to be considered in analysis. It is an area of importance which may occur more frequently as there is an expansion of the patient pool who qualify for TPIAT.

Precise patient selection for surgical procedures is key to the success of any surgical team. Screening patients who will end up with the best outcome after TPIAT will help teams continue to build on past successes and advance surgical innovation. There is recognition in this study that only patients that were determined to be fit for surgery were included. Many patients that may have been severely undernourished were excluded from this study due to not being offered the operation. Although fitness for a surgical procedure is not entirely based on nutritional status, and a poor nutritional status was not the only factor that may have excluded a patient from being included in this study, there is a small subset of patients that are not included whose information should also be considered. By understanding the individual components which play a role in making any surgery a success, a surgeon will be able to choose to perform

operations on patients who best fit criteria which has been well-established in providing guidance on selection and preparation.

FUTURE DIRECTIONS

Major abdominal surgeries like TPIAT are difficult procedures for patients. Finding ways to improve the patient experience through improving their health are pillars of medical innovation and practice. If nutrition strongly correlated with surgical outcomes for patients undergoing TPIAT, and it was shown that undernutrition has a negative impact, it could guide clinicians to begin early presurgical nutritional intervention to make TPIAT a more streamlined and successful operation. Enhanced preparation can be made through understanding the factors which impact surgical results.

With the analysis and data that has been collected, the next steps include increasing the number of patients whose nutritional assessment data is accessible for research. This can be performed in many ways. There are several centers around the United States and elsewhere which perform TPIAT. By facilitating a multi-center study focused on nutrition and its impact on TPIAT surgical outcomes and complications, increased reliability might be achieved through supporting evidence for increased nutritional evaluation. Another consideration is to allow for more time to pass and additional patients to have TPIAT performed at the Baylor Scott and White hospital system. This increased data might allow for statistical testing to have more confidence in comparing well-nourished and moderately nourished patients.

Once additional components that factor into nutrition are considered and enough data is collected with a sufficient group of patients, interventions which can modify nutrition can be studied. Such variables that might be studied include modifying the length of tube feeding

preoperatively and to evaluate if this has any impact on the clinical course or surgical complications of patients. Other oral supplements or additional caloric consumption by mouth as appropriate could also be studied and analyzed to look for trends or changes in the outcomes that patients experience and correlate with increased success of the procedure.

Another avenue that could be pursued which might provide more evidence and allow for better calculation of nutrition include more objective testing. Examples of this include bioelectrical impedance analysis and skinfold testing on patients prior to undergoing surgery. These measures work in conjunction with factors like body mass index to give a more complete picture of the nutritional status of patients and could be used to more accurately identify correlations between operative outcomes and nutrition.

CONCLUSIONS

Nutrition and its impact on patients undergoing total pancreatectomy with autoislet transplantation is a nuanced factor in surgical planning that should be more closely examined. As we have shown with our research, a sufficiently large number of patients is needed to show stronger correlations between patients who have undergone nutritional evaluations prior to surgery. Creating a larger body of data will be helpful in identifying trends that exist between surgical complications and nutrition status.

Although nutrition and caloric consumption can be modified, there are still many factors that impact the outcomes of a surgery. Having an operation like TPIAT performed at a hospital committed to providing a multi-pronged approach which includes nutritional evaluations and modification as appropriate to accelerate healing and decrease complications allows patients to receive the best possible outcomes. The hope is that this research will contribute to a heightened awareness of a variable previously considered to be minor or less important. While evaluation and stratification of risk for patients undergoing an intensive abdominal operation includes many factors, this report highlights the importance that nutrition may play in performing a successful TPIAT operation.

COMPLIANCE

This research was performed in compliance with Baylor University Medical Center's IRB procedures and obtained the required approvals. Dr. Jeanette Hasse has an established umbrella IRB protocol which covered my project, IRB #005-242. Appropriate personnel requests were obtained and no deviation from those protocols required additional IRB approval. No work was required necessitating IACUC approval. I completed both Epic and CITI trainings, in

addition to all onboarding tasks needed to perform research studies within the Baylor Scott and White system.

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