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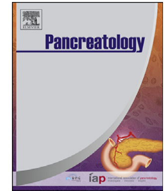

Cost-effectiveness analysis of infected necrotizing pancreatitis management in an academic setting

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ABSTRACT

Background and aims: Traditional management for infected necrotizing pancreatitis (INP) often utilizes open necrosectomy, which carries high morbidity and complication rates. Thus, minimally invasive strategies have gained favor, specifically step-up approaches utilizing endoscopic or minimally-invasive surgery (MIS); however, the ideal management modality for INP has not been identified.
Methods: A decision tree model was designed to analyze costs and survival associated with open necrosectomy, endoscopic step-up, and MIS step-up protocols for management of INP after 4 weeks of necrosis development with adequate retroperitoneal access. Costs were based on a third-party payer perspective using Medicare reimbursement rates. The model's effectiveness was represented by quality-adjusted life-years (QALYs). Sensitivity analyses were performed to validate results.
Results: Endoscopic step-up was the dominant economic strategy with 7.92 QALYs for $90,864.09. Surgical step-up resulted in a decrease of 0.09 QALYs and a cost increase of $10,067.89 while open necrosectomy resulted in a decrease of 0.4 QALYs and an increased cost of $18,407.52 over endoscopic step-up. In 100,000 random-sampling simulations, 65.5% of simulations favored endoscopic step-up. MIS step-up was favored when MIS acute mortality rates fell and when MIS drainage success rates rose.
Conclusions: In our simulated patients with INP, the most cost-effective management strategy is endoscopic step-up. Cost-effectiveness varies with changes in acute mortality and drainage success, which will depend on local expertise.
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1. Introduction

Acute pancreatitis is a critical disease leading to almost 275,000 hospitalizations within the United States(US) each year, amounting to an estimated total cost of $2.2 billion [1,2]. In approximately 20% of cases, acute pancreatitis are further complicated by tissue necrosis [3,4]. While most necrotizing cases remain sterile, one in three cases become infected [5–7]. Infected necrotizing pancreatitis(INP) carries significant morbidity and mortality, with mortality rates ranging from 11 to 39% and complications rates extending between 34 and 95% [3]. Management for patients with INP generally requires invasive intervention to achieve successful resolution.

Traditional management for INP consisted of primary open necrosectomy(ON) with wide drainage and post-operative lavage. However, due to the high morbidity and complication rate associated with the procedure, newer minimally-invasive strategies have gained favor [5]. Current guidelines favor a step-up approach, where the first step in management involves minimally-invasive drainage, either endoscopically or percutaneously [8–10].

Abbreviations: US, United States; INP, infected necrotizing pancreatitis; ON, open necrosectomy; MIS, minimally-invasive surgery; VARD, video-assisted retroperitoneal drainage; RCT, randomized control trial; QOL, quality-of-life; QALUY, quality-adjusted life-years; CT, computed tomography; OTN, open transgastric necrosectomy; IR, interventional radiology; LOS, length-of-stay; DEALE, declining exponential approximation of life expectancy; ICER, incremental cost-effectiveness ratio.

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Patients who do not clinically resolve following this stage are stepped-up to the next level of treatment involving either endoscopic necrosectomy, laparoscopic cystogastrostomy with pancreatic necrosectomy, or video-assisted retroperitoneal drainage(VARD). In the remainder of patients who still do not resolve, INP management is finally undertaken with ON as a last resort.

While there is a consensus on the benefit of a step-up approach over ON, the debate continues regarding the optimal step-up protocol between endoscopic and minimally-invasive surgery(MIS) management. Multiple randomized control trials(RCTs) have compared endoscopic and MIS step-up protocols but have not found significant differences in mortality or morbidity between the management methods [3,4,11]. Without a clear gold-standard, we sought to gain insight into the preferred management protocol by utilizing cost-effectiveness. Therefore, our study employed a decision analysis to identify which strategy, between ON, endoscopic step-up, and MIS step-up, is the most cost-effective method for the management of INP. Decision analyses allow us to quantitatively assess superiority of various comparable management modalities for diseases and are ideally suited to answering the question asked in this study. Our group has experience conducting decision analyses and have used them to identify the most cost-effective treatment modality for various diseases [12–15].

2. Methods

2.1. Decision tree analysis

A decision tree is a branching tree diagram that describes possible outcomes following a treatment decision. The analysis allows for a direct comparison of treatment pathways using treatment cost and treatment effectiveness. The tree starts with a decision node, which then branches into each of the decision pathways. Following this branch, successive branches of the tree describe outcomes associated with their respective treatment pathway. The probability of each outcome occurring is assigned to its respective branch and derived from the published literature. The cost associated with each treatment pathway, the associated outcomes, and any complications that may follow is then applied to the tree. The quality-of-life(QOL), measured in quality-adjusted life-years(QALYs), is also applied to each of the tree branches as well. Thus a model is created. Given a treatment decision and the probabilities of possible outcomes, the total cost and QALYs associated with each section of the tree is calculated and compared. Since our tree is limited to probabilities derived from the published literature, sensitivity analyses varying these probabilities are conducted to assess the validity of our results. The US healthcare system is making recent strides to practice high-value care, ensuring that the benefits of an intervention are proportional to the cost incurred. In this setting, and when the clinical benefits of one intervention over another are not apparent, a decision tree analysis provides a unique perspective. While we recognize the limitations of conducting studies in which data elements are derived from the published literature, we consider it to be a high-value low-cost method to identify regions of clinical decision-making requiring further study [16].

2.1.1. Decision tree model

Within this study, a decision tree model was designed in TreeAge(TreeAge Software, Williamstown, MA) to analyze the costs and survival associated with various management methods for INP. The costs and interventions within our model were analyzed over six months beginning with the patient's initial presentation to the hospital. The model was used to evaluate the outcomes of a theoretical cohort of patients derived from studies within the published literature. This cohort included patients with clinically diagnosed INP, defined as the presence of gas within necrotic collections on contrast-enhanced computed tomography (CT) or positive culture on fine-needle aspiration [3,4,11,17–19]. Patients included also had interventions delayed for approximately 4 weeks to allow time for the necrosis to liquefy [8,20–22]. Patients who underwent previous invasive interventions for acute, chronic, or necrotizing pancreatitis, and those without adequate retroperitoneal access were excluded [3,4,11,17–19].

The decision tree model was divided into three separate management arms: ON, endoscopic step-up, and MIS step-up protocol (Fig. 1). Although ON is no longer favored as primary management, it is still a valuable and regularly utilized treatment option in INP patient care. While different operative strategies exist beyond ON with wide drainage and post-operative lavage, including laparoscopic approaches, the literature did not provide adequate data to differentiate between modalities within the decision tree. For patients who did not resolve after a primary ON, some patients were able to be managed with non-operative therapies. The remainder of patients who could not be managed non-operatively were treated with a repeat exploratory laparotomy with further debridement or other indicated procedures. The endoscopic step-up protocol consisted of endoscopic transluminal drainage followed by endoscopic necrosectomy for those requiring further management. For the MIS step-up protocol, the primary intervention was percutaneous drainage, which was then followed by VARD, if necessary. While alternative MIS approaches exist, such as laparoscopic cystogastrostomy, VARD was selected as the only MIS management option due to the availability of high-quality data within the published literature [4,23]. Laparoscopic cystogastrostomy is preferred in situations where necrosis is limited to the lesser sac, while VARD is used in scenarios with more pervasive necrosis but requires sufficient retroperitoneal access for adequate drainage [24–26]. A combined percutaneous and endoscopic approach can also be used, whereby patients are managed initially with a percutaneous drain and then with endoscopic drainage [27,28]. The combined approach was excluded from our decision tree due to the paucity of literature describing this modality. In addition, despite evidence suggesting some patients with INP can be managed without operative intervention, there is a lack of data within the literature comparing medical to operative management. Therefore, the decision was made to exclude medical management alone from our model.

2.1.2. Parameters studied

For all three management arms, acute mortality was defined as mortality during the initial hospitalization. For patients within the step-up management arms, a subset of patients would clinically resolve after drainage and would not require further management. Those without clinical success following drainage would be stepped-up to a procedure at the next level of care. Following ON, endoscopic necrosectomy, or VARD, patients either achieved clinical success or required further management due to new complications or ongoing sepsis. Management of complications or ongoing sepsis was separated into operative management, which would include ON, open transgastric necrosectomy(OTN), and exploratory laparotomy, or non-operative management, which would include medical management and interventional radiology(IR) procedures. We predicted complications requiring operative management included ongoing INP, fistulas, or severe hemorrhage, whereas small abscesses, local hemorrhage, and wound infection could be managed non-operatively.

After designing our decision tree, data were extracted from the published literature and were subsequently used to populate the

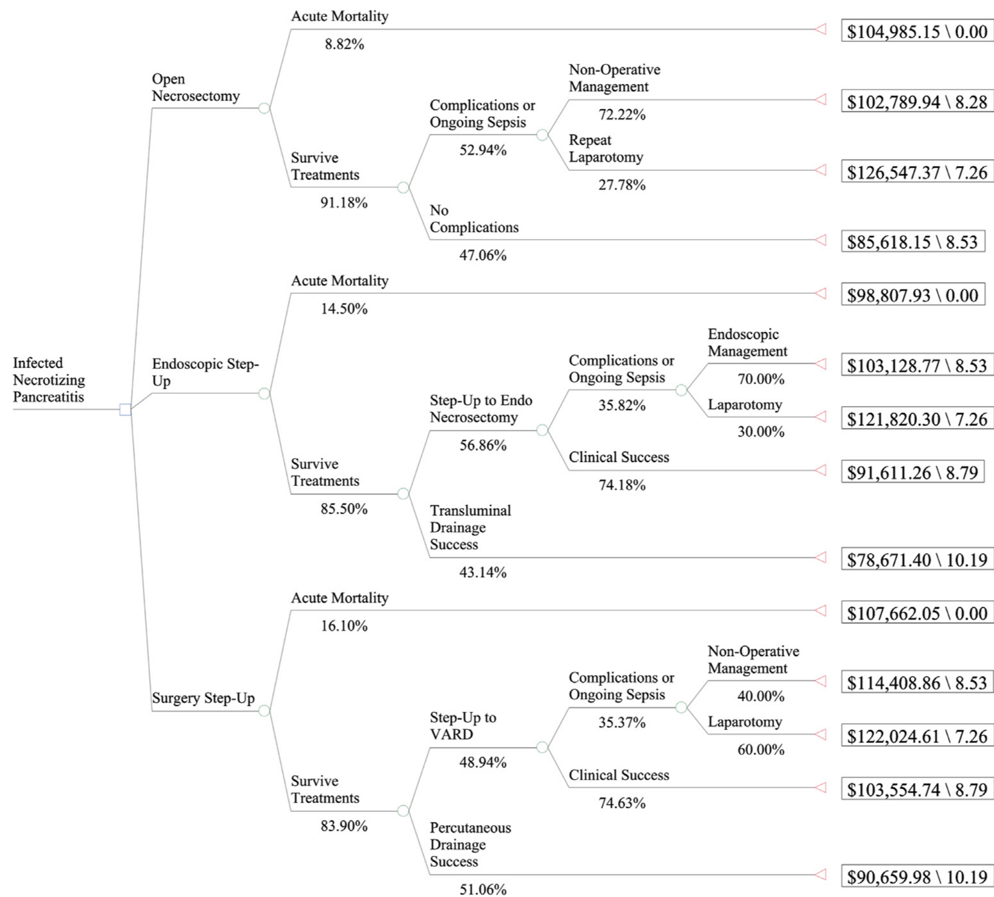

Fig. 1. Decision tree model used for analysis. The three major treatment modalities studied in our analysis and included in the tree include Open necrosectomy, Endoscopic Step-up, and MIS Step-up. Each branch point represents different outcomes the patient could encounter during treatment. Percentages included are best estimates derived from the literature. The costs in our model were derived from the Medicare Inpatient Prospective Payment System and the Medicare Physician Fee Schedule from FY2020. The effectiveness in the model was represented by quality-adjusted life-years (QALYs).

model. This data was utilized to set probabilities of downstream events occurring at each branch point on the tree. No patient data was integrated into the decision tree. Therefore, Institutional Review Board approval was not required.

2.1.3. *Costs and effectiveness*

The costs within our model were based on a third-party payer perspective, specifically Medicare reimbursement rates(US$) for physicians and hospitals. The data were derived from the Medicare Inpatient Prospective Payment System and the Medicare Physician Fee Schedule from 2020. Due to the gross variation in hospital costs across states and institutions, reimbursements were used as a proxy for hospital billing. Reimbursements should remain proportional to the final billing cost and thus was used for direct comparison between management methods. Additionally, the utilization of Medicare data allows for standardizations across the nation and increases the generalizability of our study. The cost of acute mortality was calculated as an average of the other branches in the decision tree arm because it was not possible to identify the healthcare costs accumulated before the patient died. The median length-of-stay(LOS) of ON was 60 days while the median LOS of endoscopic and MIS step-up was 35 days and 65 days, respectively. LOS values were used to calculate total hospital costs using the Medicare data.

The effectiveness in the model was represented by QALYs. A year of perfect health equates to one QALY, while death equates to zero QALYs. The declining exponential approximation of life expectancy(DEALE) method was used to calculate QALYs for the management of INP using available data on life expectancy, disease-specific mortality and morbidity, and treatment morbidity [29]. The utility weight values used in this study were based on the published literature [30,31]. Across the board, a 0.02 reduction in utility weight was used for patients who suffered complications from any of the operations in the original paper [32]; therefore, our team utilized the same assumption alongside values extracted from the published literature when assigning utility weights to arms of the decision tree.

Incremental cost-effectiveness ratio(ICER) was the primary outcome of our study. Due to the short time horizon, discounts were not utilized. The threshold for determination of the most cost-effective strategy was set as a willingness-to-pay of $100,000 for each QALY gained [33]. While the willingness-to-pay benchmark was previously set at $50,000 per QALY, we used $100,000 instead because literature strongly argues $50,000 is too low and recommends this higher and potentially more reasonable threshold [34]. Both negative ICER values or ICER values above our willingness-to-pay threshold calculated for treatment strategies represent modalities that are not cost-effective. We performed one-way, two-way, and probabilistic sensitivity analyses to test the robustness of our conclusions. The sensitivity analyses were completed employing each of the parameters within Table 2. Probabilistic sensitivity analysis was performed using 100,000 Monte Carlo simulations.

2.2. Data selection

PubMed was searched to identify relevant meta-analyses, RCTs, and cohort studies. Meta-analyses aided in the identification of additional RCTs used in conjunction with previously selected literature to build the decision tree model. Emphasis was placed on selecting studies with higher levels of evidence when available, before using data from retrospective cohort studies. Studies included are tabulated in Table 1.

Acute mortality for the step-up arms were extracted from a meta-analysis comparing endoscopic and MIS step-up methods [18]. The randomized trial by Bang et al. also included relevant data on acute mortality but the study was ultimately excluded as it was already included as one of the three trials in the aforementioned meta-analysis [18]. A modern retrospective series provided mortality, complications rates, and reoperation rates for primary ON operations secondary to INP [35]. This single-institution study, which recruited patients from 2006 to 2009, may not be generalizable to the current population of patients with INP as treatment methods may have changed in the last ten years to favor more MIS strategies.

The retrospective review by Madenci et al. reported in-hospital mortality while the meta-analyses by Bang et al. used three other RCTs reporting mortality either 6 months after randomization or 6 months after discharge [17,18]. The variability across the follow-up time after discharge in each study made it difficult to ascertain whether the three arms have truly different mortality rates.

Both step-up methods studied in our decision tree had similar designs, indications for repeat procedure, and progression to the next level of treatment [19]. Interventions were considered successful with a 10% improvement in two of three infection parameters(temperature, leukocyte count, and C-reactive protein) or improving function in at least two organ systems within 72 hours [4]. A lack of clinical improvement after 72 hours was followed by a CT, which was utilized to assess drain placement. Patients with inadequate drain placement underwent repeat drainage, while those with adequate drain placement were progressed to the next level of intervention. A recent study compared endoscopic step-up to surgical step-up and was utilized to identify clinical success rates after drainage alone and complication rates after stepping up to more invasive procedures [4]. Two literature reviews studying the outcomes of patients with necrotizing pancreatitis managed with either VARD or endoscopic necrosectomy were used to identify the mean number of procedures used to achieve clinical resolution [23,36]. The studies also provided information on encountered complications and additional procedures undertaken in the management of the patients.

Without long-term studies reporting on survival for patients treated with the various management methods investigated in this study, life expectancy for our theoretical patient population was derived from a long-term study of patients with acute necrotizing pancreatitis. A retrospective review of 167 patients at a single-center, reported an overall median survival of 9.1 years after acute necrotizing pancreatitis, which was significantly lower than the age- and sex-matched controls derived from the US population [37].

2.3. Data review and model selection

The best estimate probabilities, in addition to the high and low values, integrated into our decision tree model are delineated in Table 2. Across the three management methods, acute mortality was reported to be similar [17,18]. A similar percentage of patients managed with the two step-up protocols achieved clinical resolution with drain placement alone, and for those who did not a similar proportion of remaining patients achieved clinical success with the next step(endoscopic necrosectomy or VARD) [4,23,36]. A larger percentage of patients in the MIS step-up protocol who underwent VARD suffered complications requiring open operations when compared to patients in the endoscopic step-up protocol who underwent endoscopic necrosectomies [23,36].

Long-term survival differences between the three arms could not be elicited from the relevant literature, consequently, the same survival data was used in the decision tree for all three management methods. The reported patient population trends towards predominantly middle-aged, male patients [3,4,17,18]. Therefore, life expectancy for a 55-year-old male was used in the DEALE method(Table 1) [29]. Life expectancy for patients in this subgroup within the US is 25.52 years. Regarding morbidity, the literature demonstrated more invasive procedures carried higher

Table 1
Characteristics of studies included in decision tree.

Author	Year Published	Country	Management Modality	Study Format	Studies included	Sample Size	Mortality Rate	Drainage Success Rate	Complication Rate
Bang [18]	2019	USA	Endoscopic Step-Up	Meta- Analysis: Endoscopic vs MIS interventions	3 randomized trials	95	13.7%	Not available	Not available
Bang [18]	2019	USA	MIS Step-Up	Meta-Analysis: Endoscopic vs MIS interventions	3 randomized trials	89	13.5%	Not available	Not available
Van Brunschot [4]	2018	The Netherlands	Endoscopic Step-Up	RCT: Endoscopic Step-up vs MIS Step-up	N/A	51	17.6%	43%	Not available
Van Brunschot [4]	2018	The Netherlands	MIS Step-Up	RCT: Endoscopic Step-up vs MIS Step-up	N/A	47	12.8%	51%	Not available
Van Brunschot [36]	2014	The Netherlands	Endoscopic Step-Up	Systematic Review: Endoscopic Transluminal Necrosectomy	1 RCT, 13 retrospective cohort studies (11 non-comparative studies, two comparative studies)	455	6.1%	Not available	36%
Van Brunschot [23]	2013	The Netherlands	MIS Step-Up	Systematic Review: VARD	2 RCTs, 2 prospective cohort studies, 2 retrospective cohort studies, 1 case-matched study	128	13.3%	Not available	35%
Madenci [35]	2014	USA	Open Necrosectomy	Case Series	N/A	68	8.8%	Not available	52%

Table 2
Decision tree probabilities.

Parameter	Best Estimate	Low Value	High Value	Source
Open Necrosectomy				
Acute Mortality	8.82%	4.10%	17.94%	[35]
Complications/Ongoing Sepsis	52.94%	41.24%	64.33%	[35]
Operative Management of Complications	27.78%	15.85%	43.99%	[35]
Endoscopic Step-Up				
Acute Mortality	14.50%	8.30%	22.10%	[18]
Drainage Success	43.14%	30.50%	56.74%	[4]
Complications/Ongoing Sepsis	35.82%	31.55%	40.33%	[36]
Operative Management of Complications	30.00%	10.00%	50.00%	[36]
MIS Step-Up				
Acute Mortality	16.10%	5.00%	31.8%	[18]
Drainage Success	51.06%	37.24%	64.72%	[4]
Complications/Ongoing Sepsis	35.37%	25.89%	46.16%	[23]
Operative Management of Complications	60.00%	40.00%	80.00%	[23]

complication rates. Furthermore, procedures requiring anesthesia resulted in higher morbidity over procedures not requiring anesthesia, such as IR drainage [23,36,38].

The cost of each treatment pathway was highly dependent upon the LOS and number of repeated procedures required before clinical resolution, both of which varied across our decision tree(Table 3). Within the endoscopic treatment arm, patients who resolved with drainages received a median of one drainage procedure and those progressing to endoscopy received a median of two endoscopic necrosectomies [4]. In the MIS step-up management arm, patients who resolved with drainages received a median of three percutaneous drains and those progressing to MIS received a median of one VARD. The LOS for patients managed with a primary ON had a median of 60 days [17]. Patients in the endoscopic step-up arm had a median LOS of 35 days, while patients managed through the MIS step-up protocol had median LOS of 65 days [4]. For patients in the endoscopic arm who suffered complications requiring an open operation, a sizable increase was identified in their LOS from those who did not. Whereas patients managed with the MIS protocol, complications necessitating an open operation did not as drastically extend the LOS of patients in comparison with those who did not. The summed costs of each divergent path in the decision tree are contained in Table 3.

Table 3
Decision tree costs.

Service	Cost (US$)
Open Necrosectomy	
No Complications (Base Cost)	$85,618.15
Complication – Non-Operative Management	$17,171.79
Complication – Operative Management	$40,929.22
Endoscopic Step-Up	
Successful Endoscopic Drainage (Base Cost)	$78,671.40
Successful Endoscopic Necrosectomy	$12,939.86
Complication – Endoscopic Management	$11,517.51
Complication – Operative Management	$30,209.04
MIS Step-Up	
Successful Percutaneous Drainage (Base Cost)	$90,659.98
Successful VARD	$12,894.76
Complication – Non-Operative Management	$10,854.12
Complication – Operative Management	$18,469.87

3. Results

3.1. Base case

Endoscopic step-up management was the dominant economic treatment method for INP when compared against both MIS step-up and ON(Table 4). Endoscopic step-up resulted in 7.92 QALYs for an average total cost of $90,864.49. MIS step-up management costs over $10,000 more than endoscopic step-up while producing 0.09 fewer QALYs. As hypothesized, ON was the least cost-effective option, resulting in costs of $18,000 greater than endoscopic step-up, while resulting in 7.52 QALYs. Calculated ICER values for open and MIS step-up were negative because endoscopic step-up was the dominant economic strategy; therefore, ICER calculation were not relevant. Due to endoscopic step-up management being a dominant economic strategy, the $100,000 per QALY gained threshold was not applicable.

3.2. Sensitivity analysis

One-way sensitivity analyses were performed for each parameter within Table 2. Endoscopic step-up was consistently favored as the most cost-effective treatment strategy when altering the following variables: all ON variables, endoscopic drainage success, both MIS and endoscopic complications, and laparotomy rates. However, MIS step-up became the most cost-effective strategy when endoscopic acute mortality reached levels above 16.58%, when endoscopic drainage success fell below 30.63%, when MIS acute mortality fell below 14.03%, and when MIS drainage success rates climbed above 63.00%.

Subsequently, two-way sensitivity analyses were performed between all the variables included in our one-way sensitivity analysis. Due to the significance demonstrated in one-way sensitivity analysis, any pairing involving endoscopic step-up acute mortality, endoscopic drainage success rate, MIS step-up acute mortality, or MIS drainage success rate, exhibited scenarios wherein MIS step-up was more cost-effective than both ON and endoscopic step-up. No other combination of parameters resulted in alteration of endoscopic step-up management as the most cost-effective strategy. When examining both success rates of endoscopic and MIS drainage together, MIS step-up was more cost-effective when MIS drainage success rates rose over 20% higher than endoscopic drainage success rates (Fig. 2). ON was favored in situations when both MIS and endoscopic acute mortality rates approach 20%, when endoscopic acute mortality rates alone rose, and when endoscopic drainage success rates fell.

For the probabilistic sensitivity analysis, 100,000 random sampling simulations involving the parameters in Table 2 were performed. Results demonstrated 65.5% of these simulations favored endoscopic step-up, 31.5% of our simulations preferred MIS step-up, and the remainder(3.0%) favored ON as the primary management strategy. One thousand simulations from our analysis are

Table 4
Incremental cost-effectiveness values for base case.

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	Cost/Effect.
Endoscopic Step-Up	$90,864.09	–	7.92	0	$11,472.74
MIS Step-Up	$100,931.98	$10,067.89	7.83	−0.09	$12,890.42
Open Necrosectomy	$109,271.61	$18,407.52	7.52	−0.4	$14,530.80

portrayed in Fig. 3. Total endoscopic step-up costs ranged between $88,000-$94,00 and resulted in 7.0–8.60 QALYs. ON was generally priced at about $7000 more than endoscopic step-up and results in QALYs peaking at about 8.00. Finally, MIS step-up was demonstrated to be the costliest intervention with costs between $97,000-$104,000 and a wide range of QALYs from 6.25 to 9.00.

4. Discussion

INP is a debilitating disease, with a high morbidity and mortality rate, generally requiring invasive intervention for clinical resolution [3,4]. Currently, step-up strategies gained favor as the management of choice for these patients due to better outcomes over ON, however, multiple step-up protocols exist [8–10]. Studies evaluating step-up protocols have not yet established a significant difference in terms of acute mortality, complications, or clinical success [3,4,11,39]. Without a clear disparity in outcomes, a gold standard does not exist, leaving management to the discretion of the surgeon depending on the availability of resources. Therefore, in the absence of an optimal management strategy, we sought to determine which step-up protocol, between endoscopic or MIS step-up with VARD, was more cost-effective.

Utilizing a decision analysis for patients with INP, this study demonstrated that endoscopic step-up is the dominant economic strategy over MIS step-up and ON. MIS step-up was about $10,000 more expensive than endoscopic step-up and resulted in fewer QALYs likely due to the longer LOS and the increased number of procedures associated with the clinical resolution of the disease when compared with endoscopic management [40,41]. Additionally, a smaller percentage of patients treated with the endoscopic step-up pathway were converted to open operations when compared against MIS step-up [23,36,42]. Despite the identification of endoscopic step-up management as a dominant economic strategy, our study showed in scenarios where MIS acute mortality rates fell or endoscopic acute mortality rates rose, MIS step-up was preferred. Furthermore, when MIS step-up drainage success rates improved and endoscopic step-up success drainage rates declined, MIS step-up was again preferred. In scenarios where acute mortality for MIS step-up is significantly reduced or where endoscopic step-up acute mortality is increased, we can expect a noticeable improvement in the QALYs for the MIS step-up treatment arm over endoscopic step-up. Moreover, if MIS drainage rates significantly improve, fewer patients in this treatment arm will be stepped up to VARD and then potentially more invasive operations. Fewer invasive operations will result in cheaper treatment costs which will also be associated with improved QOL metrics in the short-term over patients who eventually undergo open operations [43]. Depending on local expertise and available resources, there may be scenarios where ON is a cost-effective management modality but across our simulated patient set this was an uncommon occurrence. In situations where all three modalities are feasible options for patients, we recommend endoscopic treatment because we found it to be the favored modality from not only a cost perspective but also outcome and patient perspective.

While Treeage was the software utilized in this study, there are other options for running decision tree analyses. TreeAge has an excellent visual interface which simplifies tree construction and a comprehensive user manual which allows for troubleshooting [44]. Excel can be used for these analyses but is better suited for trees less complex than the one designed for this analysis [45]. To better accommodate more complicated analyses, TreeAge was chosen over Excel by our research group. MATLAB and R are two other programs regularly used to conduct decision tree analyses; however, they both require more extensive programming experience and complex mathematical expertise which makes for a more significant learning curve. While MATLAB and R are capable of improved plotting capabilities and much wider extensibility by way of add-on packages, our group did not find these customizable features essential enough to justify using them over TreeAge.

While several cost-effectiveness studies have examined different management options for patients with INP, a review of the literature revealed our study to be the first decision analysis completed. Similar to our study, van Brunschot et al. identified endoscopic step-up as the more cost-effective strategy in comparison to MIS step-up with a median cost of €60,228 for patients in the endoscopic step-up arm and a median cost of €73,883 for patients in the surgical step-up protocol when evaluating the cost of care for six months [4]. When evaluating the long-term costs associated with INP management, Holleman et al. found yearly medical costs were not significantly different between patients managed by surgical step-up or ON [46]. Thus, this study conveys long-term morbidity, and rehospitalization rates are similar between the different management options. This further suggests the initial hospitalization period is the most substantial factor when evaluating differences in management costs for patients with INP.

In the last decade, the field has shifted towards more conservative management approaches for INP. Most recently, literature reports on the success of nonsurgical management with the use of antibiotics, nutritional support, and drainage [47]. This management strategy has shown success in 64% of the patients studied in a meta-analysis and also obviates the morbidity and mortality of surgical necrosectomies; however, we were unable to find literature comparing nonsurgical and surgical interventions. We believe such a strategy would simultaneously greatly decrease the morbidity and costs commonly associated with surgical treatment. While a cheaper strategy involving nonsurgical treatment has merits, there are scenarios where nonsurgical modalities will not be sufficient.

To design a model highlighting only the most relevant components within the management of INP, decisions had to be made regarding what should be included within the decision tree, particularly due to limitations with the availability of data in the published literature. The most notable of which was our decision to exclude laparoscopic cystogastrostomy as an additional management arm due to the operation being an understudied method for the management of INP. The first laparoscopic transgastric, retroperitoneoscopic, and retrocolic procedures were described in 1996 but since then have been mostly overshadowed by VARD for the management of acute necrotizing pancreatitis and INP [48]. A recent case series of 28 patients reported a 3.6% postoperative mortality, a 28.6% rate of pancreatic fistula development, and a 10.7% rate of recollection identified at the three-month follow-up

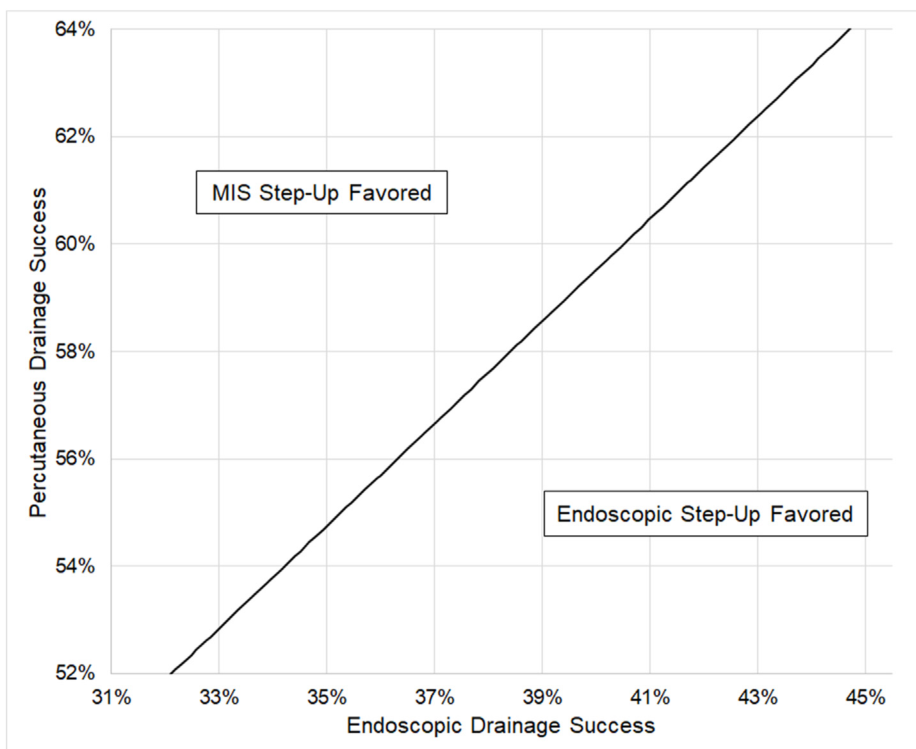

Fig. 2. Two-way sensitivity analysis of drainage success rates of endoscopic step-up and MIS step-up. The line represents points at which the two treatment modalities are equally cost-effective. Points above the line favor MIS step-up and points below the line favor endoscopic step-up.

Fig. 3. Scatterplot of the first 1000 of 100,000 Monte Carlo probability simulations. Only the first 1000 simulations are shown for improved visualization.

[49]. Laparoscopic management appears to be associated with many of the benefits of VARD management of INP and may represent a viable alternative in situations where endoscopic management is not appropriate or feasible, however, further evaluation in the form of prospective studies and RCTs would be necessary to prove this theory. Additionally, due to the lack of data in the literature, we did not study the differences between stent types. OTN is a newer technique which is uncommonly used as a

single-stage procedure in the management of INP [50]. It is currently not included in step-up INP management guidelines as a treatment option, so we chose not to include OTN as an alternative to ON and exploratory laparotomy after failed initial ON. While recent studies show OTN can have better morbidity values than ON, this fairly novel management method is understudied and no proven difference exists [51].

Furthermore, another key element in the design of our decision tree requiring further discussion is the definition of acute mortality. Within our decision tree, acute mortality is an all-encompassing parameter that captures mortality at any point in management. In reality, mortality could occur at any intervention level, with some patients succumbing to the disease before invasive management. However, due to limitations within the available literature, there was not enough information to distinguish mortality at various points in the patient care pathway. While pooled mortality rates have been demonstrated to be similar between endoscopic step-up and MIS step-up, individual components have yielded different mortality rates, such as endoscopic necrosectomy having a post-operative mortality rate of 6% and VARD yielding a postoperative mortality rate of 13% [23,36]. Higher mortality rates earlier on within the step-up pathway would result in more significant changes within the analysis as a result of the greater subset of patients affected. Therefore, if endoscopic transluminal drainage carries a higher mortality rate than percutaneous drainage, MIS step-up can be more cost-effective. Within our study, this was highlighted by manipulation of the mortality rates, where MIS step-up became the more cost-effective option at high endoscopic mortality or low MIS mortality. Similarly, in scenarios where endoscopic and MIS mortality rise above ON mortality rates, when endoscopic mortality rates are elevated, and when endoscopic drainage success rates are diminished, we found that ON was identified as the most cost-effective option. In health systems with less experience using the endoscopic management of INP, MIS step-up would be more likely to be preferred and *vice versa*. As such local expertise should be a primary consideration when deciding upon the management modality.

Although our study utilized sensitivity analyses to test the robustness of our results, it should be acknowledged certain components within our study limit the strength of our conclusions. First, our analysis is subject to publication bias as the field is understudied. However, a majority of the studies and data used in our decision tree model was abstracted from the same group, the Dutch Pancreatitis Study Group, which could reduce the generalizability of our study at non-academic centers. Furthermore, many of the studies involve small cohorts due to the nature of the disease, resulting in greater variance in outcomes. Despite the movement away from ON usage in the management of INP, recent literature suggests primary ON may be amenable for the treatment of a specific population without comorbidities and preoperative risk factors [52]. Due to limitations in data, we were unable to stratify our hypothetical patient population by risk factors to identify if this conclusion holds in our study. Finally, we did not run a test set on our model using real patient data from our institution to further the strength of our model due to the lack of accessible patient data with which to design a test. Our institution still rarely sees INP cases and does not currently have a INP database which would allow us to create and run a test set using our cost-effectiveness model.

Internationally, healthcare costs and overall life expectancy can vary from country to country. While much of our data was derived from studies conducted in the Netherlands by the Dutch Pancreatitis Study Group, our study utilized Medicare healthcare costs and US life expectancy data which is a limitation. Without treatment cost data from various countries, our results are not generalizable to other countries. However, Van Santovoort et al. reported on the mean total cost of ON and MIS step-up approaches in 2010 [17]. In this study, the mean cost of ON was $131,979(€89,614) and the mean cost of MIS step-up approaches was $116,016(€78,775). While these values are quite close to costs reported in our trial and differ by a similar margin, the study did not report on endoscopic step-up methods costs which would be necessary to run our analysis using Dutch costs to see if our conclusion remains consistent. However, using the information available at this time, we assume our conclusion will hold true in various health systems across the globe, especially in the Netherlands.

Lastly, our decision tree model is designed to be generalized and may not be appropriate for each case seen by every individual practice. Some patients may do well with a primary ON or even nonsurgical treatment; likewise, some practices may not have the resources to properly implement a step-up protocol for every patient so physicians must separately evaluate each patient to identify if our overall recommendation applies. Local expertise and costs at various health systems should therefore influence decision making when choosing optimal treatment modalities. Additionally, each patient will present differently and will vary in the severity of the disease. As mentioned previously, further prospective studies and RCTs would be of interest in order to fully elucidate the differences in clinical outcomes between the various management methods and provide better insight into the optimal treatment algorithm for INP but will be difficult to coordinate due to the complicated management of this disease and the relative rarity of the disease. In the meantime, the design and implementation of novel treatment algorithms will improve the management of this disease.

Author contributions

All authors contributed to the conception and design, acquisition of data, analysis, and interpretation of data, editing, and final approval. VP and PLQ contributed to the drafting of the article. The critical revision of the article was performed by SA, JBO, SKA, and RJC.

Disclosures

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Presentation

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Declaration of competing interest

Vishnu Prasath, Dr. Patrick L. Quinn, Dr. Joseph B. Oliver, Simran Arjani, Dr. Sushil K. Ahlawat, and Dr. Ravi J. Chokshi have no conflicts of interest or financial ties to disclose.

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