**Outcomes from Minimal Access Retroperitoneal and Open Pancreatic Necrosectomy in 394 patients with Necrotizing Pancreatitis**

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**Mini-Abstract**

 This is a single center experience in 394 patients with severe necrotizing pancreatitis, of whom 274 initially had minimal access retroperitoneal pancreatic necrosectomy (MARPN) and 120 had open necrosectomy. The overall mortality rate decreased between the periods 1997-2008 (23.8%) and 2009-2013 (11.2%) but MARPN independently reduced mortality risk by 73%.

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**STRUCTURED ABSTRACT**

**Objective**: To examine the outcomes from minimal access retroperitoneal pancreatic necrosectomy (MARPN) and open pancreatic necrosectomy (OPN) for severe necrotizing pancreatitis in a single center.

**Summary Background Data:** The optimal management of severe pancreatic necrosis is evolving with few large center single series.

 **Methods**: Between 1997 and 2013, patients with necrotizing pancreatitis at the Liverpool Pancreas Center were reviewed. Outcome measures were analyzed by intention to treat.

**Results**: There were 399 patients that initially had either MARPN (274, 69.5%) or OPN (120, 30.4%); missing data in five (1.3%). Overall complications occurred in 174 (63.5%) patients who had MARPN and 98 (81.7%) in OPN (p<0.001); OPN was associated with increased postoperative multi-organ failure (42 (35%) vs 56 (20.4%), p=0.001) and median (inter-quartile range, IQR) APACHE II score (9 (6-11.5) vs 8 (5-11), p<0.001) with intensive care required less frequently in MARPN patients (40.9% (112) vs 75% (90), p<0.001). The mortality rate was 42 (15.3%) in MARPNs and 28 (23.3%) in OPNs (p=0.064). Both the mortality and the overall complication rates decreased between 1997-2008 and 2008-2013 (49 (23.8%) vs 25 (11.2%) p=0.001 respectively; 151 (73.3%) vs 121 (64.4%), p=0.080 respectively). Increased mortality was independently associated with age (p<0.001), preoperative intensive care stay (p=0.014) and multiple organ failure (p<0.001), operation before 2008 (p<0.001) and conversion to OPN (p=0.035). MARPN independently reduced mortality risk (Odds Ratio=0.27; 95% CI=0.12-0.57; p<0.001).

**Conclusions**: Increasing experience and advances in perioperative care have led to improvement in outcomes. The role of MARPN in reducing complications and deaths within a multimodality approach remains substantial and should be used initially if feasible.

**INTRODUCTION**

Pancreatic necrosis develops as a consequence of acute pancreatitis in approximately 20% of patients with infection occurring in around 30% of these cases (range 14-62%)1-7. Infected pancreatic necrosis is associated with 8-39% mortality rate and substantial morbidity1-8. Persistent organ failure beyond 48 hours is the major cause of morbidity occurring in around half of patients with pancreatic necrosis and in up to two thirds of those with superimposed infection**3-9**. Unlike sterile necrosis, infected necrosis generally requires intervention in the form of debridement and/or drainage either surgical or radiological 7-10.

During the past two decades the surgical management of infected or potentially infected pancreatic necrosis has undergone considerable changes. Percutaneous catheter drainage, minimally invasive retroperitoneal pancreatic necrosectomy (MARPN), the step-up approach and endoscopic transgastric procedures, have all been proposed as alternatives to open pancreatic necrosectomy (OPN)10-21, but the optimal approach addressing pancreatic necrosis cannot be accurately predicted upfront. In a prospective multicenter study15, 62% of patients with acute necrotizing pancreatitis were adequately managed without any kind of intervention but only 33% of the patients had infected pancreatic necrosis. In a recent systemic review16 it was suggested that up to 64% of patients with infected pancreatic necrosis could be managed by non-surgical intervention but all the studies were highly heterogeneous. In another systemic review17 percutaneous catheter drainage allowed surgical debridement to be avoided in 55.7% of cases. Consequently, the role of surgery as an initial procedure in necrotizing pancreatitis has been progressively called into question. Recent IAP/APA guidelines18 suggested percutaneous catheter drainage or endoscopic transmural drainage to be the first step in the treatment of infected necrotizing pancreatitis.

Debridement of infected pancreatic necrosis however, continues to be the mainstay of treatment when percutaneous drainage fails, which is the case in 25% to 75% of patients10, 13,,19-22. OPN is a associated with 34-95% morbidity and 6-25% mortality depending on the series, existing expertise, and the severity of illness at the time of surgery2,8,11-13,20, 22-24. The experience from OPN has shown that failure to adequately control infected pancreatic necrosis results in a very high mortality, which to a <20% mortality rate achieved with successful surgical debridement2,8,11-13. Improved technologies have enabled the development of increasingly minimally invasive procedures. Retroperitoneal video assisted necrosectomy has been performed with 0-20% mortality and 10-30% complication rate10,12,13,17,25-30. We have previously demonstrated the significant benefits of MARPN compared to OPN in terms of morbidity and mortality10. Both modalities have been used in the Regional Pancreas Unit associated with the National Institute of Health Liverpool Pancreas Biomedical Research Unit to treat patients with pancreatic necrosis who were referred to or admitted to our Unit with severe acute pancreatitis. The purpose of this study was to reassess patient outcomes following MARPN or OPN on an intention to treat basis and identify predictors of death and postoperative complications.

**PATIENTS AND METHODS**

All patients undergoing pancreatic necrosectomy in the Regional Pancreas Unit at the Royal Liverpool Hospital were recorded in a prospectively kept electronic database. Data the from 1st January 1997 until the 31st December 2013 were used in this study. Patient characteristics and disease severity have been kept up to date according to revised disease severity classifications by going through individual patient notes. Patient demographics, preoperative, operative, interventional radiology and postoperative data as well as the duration of hospitalization and intensive therapy unit (ITU stay) were retrieved. Preoperative data analyzed included the initial and immediate preoperative computed tomography (CT) severity index (SI)31, the Acute Physiology and Chronic Health Evaluation (APACHE) II score,32 and organ dysfunction score33,34. Physiological and organ dysfunction scores were repeated 24 hours postoperatively. Severe acute pancreatitis was defined by the 2012 Atlanta classification35. Outcome measures included overall as well as procedure related complications and mortality. Mortality was defined as death during admission or during the 3 months after discharge. Operation specific complications include bleeding, pancreatic fistulas, biliary strictures or leaks, gastrointestinal or bowel leaks, ischemic gut, wound complications, intra-abdominal abscesses, pseudo-aneurysms and portal vein thrombosis developing in the postoperative period. All remain complications were categorized as operation non-specific.

The overall management plan as well as the indication, type and timing for any kind of intervention was set in the benign pancreas Multi-Disciplinary Team (MDT) meeting by a panel of specialist pancreas consultant surgeons, radiologists and gastroenterologists. Patients were escalated to a critical care setting for intensive organ support and monitoring whenever required. Surgical intervention no earlier than 4 weeks after symptom onset was intended unless the clinical state of the patient necessitated earlier necrosectomy. Patients with severe acute pancreatitis35 were managed according to the initial 20021 and revised 2013 IAP/APA evidence based guidelines18. Endoscopic sphincterotomy was performed early in patients with biliary pancreatitis admitted with or developing acute cholangitis.

A multi-detector contrast enhanced CT scan using a pancreatic protocol was undertaken in all patients within 72-96 hours from symptom onset or from hospital admission when the time of onset could not be verified. In patients with diagnostic uncertainty such as suspicion for visceral perforation or ischemic gut a CT scan was undertaken immediately on hospital admission. A repeat CT scan was undertaken as dictated by the patient’s clinical condition, inflammatory markers, or whenever an invasive intervention was considered. A CT guided fine needle aspiration for bacteriology (CT-FNAB) was advocated for most patients with >30% pancreatic necrosis and no gas, failing to improve after > 4 weeks of supportive care (or less if clinically indicated). Aspirates were sent for Gram staining, bacteriology, and fungal culture. Positive stain or cultures were indications for urgent necrosectomy. Infected necrotic tissue was defined as: i) a positive FNAB from pancreatic or peripancreatic necrosis, ii) a positive sample retrieved during a drainage procedure or a pancreatic necrosectomy, or iii) the presence of extraluminal gas in a fluid collection or the retroperitoneum on contrast-enhanced CT. Suspected infected necrosis was defined as, positive blood cultures, persistent sepsis syndrome or progressive clinical deterioration despite maximal support in the ITU, without documentation of infected pancreatic necrosis.

Patients with sterile pancreatic necrosis also underwent pancreatic necrosectomy if they were unable to eat due to persistent pain and vomiting after four-six weeks or more hospitalization despite perseverance with nutritional support. Patients showing improvement were discharged and followed up for recurrent symptoms or the development of medium and late complications25.

***Surgical and Interventional Techniques***

**Minimally invasive retroperitoneal pancreatic necrosectomy (MARPN).** This were performed as previously described10,13.25.36. Briefly access to the necrotic cavity was customarily obtained via the left flank with a 12F pigtail catheter inserted under CT-guidance. The path of choice was through the area extending between the lower pole of the spleen and the splenic flexure. In patients with significant (right-sided) pancreatic head necrosis not amenable to left sided MARPN an anterior duodenal path through the gastrocolic omentum was established and bilateral or right sided procedures were subsequently performed. In patients with pancreatic necrosis tracking down to the left and/or right retroperitoneal gutters a second left sided drain was introduced in order to be later used as an accessory track for video assisted pancreatic necrosectomy. Patients with right sided MARPNs as well as those with necrosectomies performed though more than one access sites were categorized as complex MARPNs. With the guide wire in place the patient was transferred to the operating theatre and properly positioned to so that the access track was approximately horizontal. Depending on the general condition of the patient the procedure was conducted under general anesthesia or just sedation. Under fluoroscopy the catheter was exchanged over a guide wire and serial dilatations up to 30F were routinely performed. An operating nephroscope with a wide-bore operating channel was used for piecemeal removal of pancreatic necrosis and samples were sent for microbiology. Initial debridement was usually restricted by predominant immature necrosis and oozing from the cavity walls. Following a first time MARPN, an irrigating drain, consisting of a 28F chest drain and a 10F nasogastric tube sutured together, was inserted into the cavity and 0.9% saline solution used to irrigate the cavity continuously at a rate of 125 mL/h. There were two new modifications form that previously mentioned10. (1) The guide wire was kept in place during the whole procedure including the necrosectomy itself and placement of the irrigating drain in order to avoid the risk of losing the access track. (2) The outer sheath of the nephroscope was removed to enable larger pieces of necrosis to be removed with the grasping forceps. The MARPN session was then repeated at approximately 7-10 day intervals until all the necrosis had been removed and only healthy granulation tissue could be visualized. Improvement based on the patient’s clinical condition, CT imaging and laboratory values, the irrigation rate was progressively halved to 30 mL/h then discontinued. A fistulogram was performed to show complete collapse and control of the cavity. The drainage catheter was then downsized using a small nasogastric tube and the patient was discharged home under district nurse care and followed up at 21 day intervals with drain shortening on each visit.

**Open pancreatic necrosectomy (OPN).** This was performed with postoperative local lavage was undertaken as previously described by Beger et al.37. Postoperative closed irrigation was performed with at least two wide bore drains similar to those described for MARPNs which were placed in the necrotic cavity through separate small incisions. Packing of the abdomen was not routinely employed. Second look OPNs were reserved for patients who developed specific serious complications of pancreatic necrosis such as ischemic gut.

**Interventional drains.** Additional radiologic drains were inserted to drain loculated residual fluid collections, areas of evolving necrosis, or symptomatic ascites irrespective of the type of initial treatment.

**Endoluminal ultrasound (EUS) guided procedures.** In a minority of patients EUS guided endoscopic pancreatic necrosectomy was performed as an index procedure for walled off pancreatic necrosis. All operations were performed by a single endoscopist using a standard technique in order to achieve access to the pancreatic necrotic cavity21,38. Once the communication between the stomach and the walled off necrosis was established a balloon dilatation was performed and a 12 mm, 2-3 cm covered metal stent with flared ends was deployed in order to maintain track patency and active endoscopic removal of debris was performed using snares and forceps. No pigtail or naso-pseudcystic drains were left in situ postoperatively and the necrotic cavity was not kept on postoperative irrigation. No repeat sessions were performed.

 **Statistical Analysis**

Outcome measure comparisons between MARPN and OPN were performed by intention to treat. In order to take into account general improvements in patient care a time variable was introduced before and after 2008 with a similar number of patients in each period and coincided with our previous report10. Frequency counts and percentages were used to summarize categorical variables and median and inter-quartile range (IQR) for continuous variables. Fisher’s exact test and the two-tailed Mann-Whitney U test were used to identify significant differences between groups of patients for categorical and continuous variables respectively. Univariable logistic regression analysis was performed to identify preoperative risk factors associated to mortality and overall complication rate and all risk factors reaching a univariate analysis p-value <0.1 were included in a multivariable logistic regression analysis. A stepwise selection process was used to identify risk factors independently associated to mortality and overall complication rate and estimate their effect. No imputation was performed for missing data. Analysis was performed on an available case basis using software R version 3.0.1 39 and significance level of a = 0.05 was applied for all statistical tests.

**RESULTS**

**Demographics, etiology and preoperative findings.** There were 399 patients with acute necrotizing pancreatitis who underwent pancreatic necrosectomy during the study period but five were excluded because of incomplete data. There were 206 patients treated before 2009 and 188 after this time point. MARPN was performed in 274 patients (69.5%) while 120 patients (30.5%) had an OPN (Table 1). The preoperative CT severity index was significantly higher in patients submitted to MARPN compared to those who had OPN (9 vs 8, p<0.001), while more MARPN patients had > 50% pancreatic necrosis on preoperative imaging (51.1% vs 32.5%, p<0.001). There was no difference in preoperative APACHE II scores, the prevalence of preoperative MOF or the need for preoperative ITU stay between the two groups. MARPN patients however tended to spend significantly more time in ITU preoperatively (median of 14 vs. 8 days, p=0.039). Overall, 289 patients were tertiary referrals (73.4%) with the transfer being made in a median of 16 (7.5-30) days from the index admission. More of the tertiary referrals were treated with MARPNs compared to OPN (213 (77%) vs 76 (63.3%), p=0.005). Biliary stones and excessive ethanol consumption were the two principal etiologies of acute pancreatitis (n=289, 73.4%).

There were 166 (42.1%) patients who were operated for infected necrosis confirmed preoperatively, 47 (11.9%) patients were operated for acute systemic deterioration due to sepsis and 153 (38.8%) patients were operated for a complicated pancreatic necrosis and extra-pancreatic necrotic fluid collections. These patients who failed to improve under conservative/non-invasive management, developed local complications from an enlarging acute or walled off pancreatic necrosis, had persistently elevated inflammation markers despite optimal care. Patients who underwent MARPN more frequently had CT- FNAB confirmed infections compared to patients who had OPN (34.3% vs. 12.5%), while complicated necrotic collections and pancreatic necrosis with gas were both commoner indications among patients having an OPN (46.7% vs. 35.4% and 19.2% vs. 12.4%, respectively) with an overall p<0.001.

**Post-operative outcomes.** Infected pancreatic necrosis was confirmed in 306 pancreatic necrosectomy specimens (77.7%), and were significantly more frequently encountered in patients submitted to MARPN (83.2% vs. 65%, p<0.001) (Table 2). Of the 274 patients in whom an MARPN was attempted, 36 (13.1%) required conversion to an open necrosectomy. Poor access to the necrotic cavity and inability to dilate the track was the reason in 16 patients, while in eight patients there was bleeding (during the initial or the repeat MARPNs) which could not be controlled by conservative measures or interventional radiology, in six patients there was a perforation either into a hollow viscous or into the peritoneal cavity, in four patients the debridement achieved was suboptimal and two patients developed ischemic colitis requiring urgent colectomy. All 36 patients were included in the MARPN group of patients on an intention to treat basis.

Five of the 120 patients who had an OPN required additional MARPN procedure to completely remove remaining pancreatic necrosis, and were included in the OPN group by intention to treat. All five patients had their index procedure in the referring center prior to being transferred to our Unit. In two more patients a laparotomy was done in the referring center, but no necrosectomy was performed at that time. Both patients were deemed suitable for MARPN based on subsequent imaging and were categorized as MARPNs on an intention to treat basis.

A median (IQR) of 3 (2-4) MARPNs were performed. Difficult cases required more complex MARPN procedures to be performed or additional abdominal drains to be inserted. In nine (3.3%) patients bilateral MARPNs needed in order to achieve adequate access to the pancreatic necrosis. In six (2.2%) patients two left sided drains were inserted towards the necrotic cavity and video-assisted necrosectomies were later performed from both tracks. One (0.8%) patient had a right sided access to the pancreatic necrosis and an ipsilateral video assisted necrosectomy was performed. This patient had had initially an OPN which yielded unsatisfactory results. Percutaneous interventional radiology drains additionally had to be inserted for intra-abdominal collections in 80 (29.2%) MARPN and 26 (21.7%) OPN cases. EUS-assisted endoscopic pancreatic necrosectomy was performed in acutely in three (0.76%) patients. Two of them were converted to MARPN owing to technical failure and the third was converted to OPN. Six more EUS drainage procedures were performed <1 year from the index (MARPN) procedure in order to treat symptomatic recurrent walled off necrosis, successfully in three.

Postoperative mortality was higher, though not significantly, in patients undergoing OPN compared to MARPN (23.3% vs 15.3%, p=0.064). OPN was associated with higher overall (81.7% vs 63.5%, p<0.001) and procedure related complication rate (51.7% vs 35.4%, p<0.001). Postoperatively, 98 (24.9%) patients had multiple organ failure (MOF) with a median APACHE II score of 8 (2-14). Postoperative multiple organ failure was associated more frequently with OPN compared to MARPN (35% vs. 20.4%; p=0.001), with OPN patients having higher postoperative median APACHE II scores (9 vs. 8, p<0.001). A higher proportion of OPN patients required ITU admission than patienst who had MARPN (75% vs. 40.9%, p<0.001) but ITU stay was longer in the latter (12.5 days vs 6 days, p=0.018) reflecting the preoperative state. MARPN patients required significantly more prolonged total hospitalization (98 days vs 71 days, p<0.001). Specific complications, persistent pancreatic fistulas (11.7% vs 5.1%, p=0.032) and postoperative sepsis with MOF (25% vs 12%, p=0.003) were significantly more prevalent following OPN, while MARPNs were associated with significantly higher postoperative DVT rates (6.6% vs 1.7%, p=0.046) (Table 3).

**Comparison of outcomes between 1997-2008 and 2009-2013.** There was a significant decrease in mortality rates after 2008 falling from 23.8% to 11.2% (p=0.001) (Table 4). There was also a significant decline in operation non-specific complications (13.8% vs. 27.2%, p=0.001) and a smaller reduction in the overall (64.4% vs. 73.3%, p=0.080) and procedure related morbidity (41.5% vs 44.6%, p=0.543). There was a decrease in the median duration of hospitalization (88 days vs. 96 days, p=0.015). There was a rise in the proportion of OPNs undertaken (34% vs. 27.2%, p=0.155), a decrease in the procedure conversion rate (7.4% vs. 10.7%, p=0.141) and a wider application of complex MARPNs (5.3% vs 2.9%, p=0.580) as well as an increase in the postoperative application of percutaneous radiologic drains (36.7% vs 18%, p=0.601). A lower proportion of patients with preoperative MOF (20.2% vs. 27.2%, p=0.029) or >50% pancreatic necrosis (38.3% vs 51.9%, p<0.001) were submitted to a pancreatic necrosectomy after 2008 with higher prevalence of postoperative MOF (35% vs. 20.4%, p=0.001). While before 2008, FNAB confirmed infected pancreatic necrosis was the primary indication for intervention (34%), complicated necrotic collections were the main indication for necrosectomy after 2008 (51.1%) (p< 0.001) (Table 5).

**Univariate and multivariate logistic regression analysis.** The results of the univariate logistic regression analysis for complications and mortality are summarized in Table 5. Increased risk of complications was associated independently with increasing patient age (p=0.015), male gender (p=0.006), tertiary referral (p=0.015), preoperative ITU stay (p<0.001), insertion of additional percutaneous radiologic drains (p<0.001) and conversion to OPN (p=0.005) whilst independent complication risk reduction was associated with use of MARPN (p<0.001), (Table 6). Increased mortality was independently associated with increased patient age (p<0.001), preoperative ITU stay (p=0.014), preoperative MOF (p<0.001) and conversion to open necrosectomy (p=0.035) and independent mortality risk reduction was associated with admission after 2008 (p<0.001), and use of MARPN (p<0.001), (Table 6).

**DISCUSSION**

A very high proportion of our patients were tertiary referrals, representing 289 (73.4%) out of 394 patients treated, with the more conservative approaches not being suitable or having already been utilized before transfer. There was a general reduction in mortality between the earlier and later time periods, reflecting newer techniques and a more integrated approach. Nevertheless MARPN was the only independent factor associated with a significant reduced risk of mortality with an estimated 73% risk reduction. This was also observed in relation to complications with MARPN being the only independent factor associated with a similarly large complication risk reduction.

Infected pancreatic necrosis, acute complications not amenable to interventional radiology and deteriorating organ failure in patients with necrotizing pancreatitis are potentially life threatening complications of acute pancreatitis which require intervention1,4,5,7,9,18. Apparently sterile but highly symptomatic necrosis, manifesting as disabling pain, gastric outlet or biliary obstruction, or failure to thrive, represent further indications for catheter drainage, or a debridement procedure9,18,40. Pancreatic necrosis can be managed by many different techniques including open necrosectomy and closed packing41, laparoscopic transperitoneal necrosectomy42, minimal access retroperitoneal (video assisted) necrosectomy10,12,13,17,25-30, endoscopic necrosectomy**24,43,44** or drainage45, or step-up combination approaches using percutaneous techniques and surgery 20, or transmural drainage and endoscopic necrosectomy46. When the intended benefits from simple drainage of an acute necrotic collection are poor however, surgical debridement should be implemented as soon as possible. The two approaches that have risen to favor in this regard, are the retroperitoneal route (MARPN) 10,12,13,17,25-30  and the endoscopic transgastric necrosectomy**24,43-45**.

When debridement is not amenable to a minimally invasive technique due to poor radiologic access, for other technical reasons, or when other acute intra-abdominal conditions come into play, patients were reassigned to OPN. Complex variations to the classic MARPN including bilateral, multiple unilateral and right-sided procedures have been increasingly performed during the past few years in our Unit in an effort to minimize the need for OPN. Similarly, postoperative percutaneous catheter drainage has customarily been used to help manage infectious sequela following both types of pancreatic necrosectomy. Endoscopic drainage and necrosectomy have been introduced but with limited success in this group of patients. Infected pancreatic necrosis was found in 77.7% of our patients and 83.2% of those undergoing MARPN justifying our decision to perform a necrosectomy2,6,41,47,48 while the CT-SI score6,11,20, the APACHE II score6,11 and the prevalence of MOF6,15 reflect the severity of acute pancreatitis in our series. In addition to a reduced overall complication rate MARPN was associated with significantly lower operation specific complication rates.

As well as a general reduction in mortality between the two periods, there was been a steady decrease in the operation related morbidity and in the operation non-specific complication rate. This means that there was improvement from OPN in keeping with other studies12,23,49-51 . Nevertheless patients undergoing MARPN had more severe disease based on preoperative imaging and postoperatively MOF was more common and median APACHE II score was higher following OPN. These findings demonstrate the detrimental effect of OPN on organ function. Since our study is very large and is from a single center it can compare OPN with MARPN taking into account preoperative risk factors and clearly shows that MARPN is the procedure of choice, although technically this is not possible for mainly access reasons in around 30% of cases.

Our study provides an updated comparison of short-term outcomes between MARPN and OPN in patients with necrotizing pancreatitis. Despite the obvious advantages of MARPNs, this later period of our work has been associated with further decline in postoperative mortality, highlighting a wide margin for quality improvement especially in patients submitted to OPN. In a group of patients who have been principally admitted to another hospital and referred to our Unit for definitive treatment, complex MARPNs, postoperative insertion of percutaneous catheters and conversion from one type of necrosectomy to the other, as well as liberal repetition of MARPNs until necrosis-free pancreatic margins are achieved, suggest some of the technical reasons for this improvement. Further refinements in the MARPN technique, increasing application of endoscopic necrosectomies as well as the introduction of hybrid step up approaches may provide even better results in the future.

**LEGENDS FOR TABLES**

**Table 1**. Demographic and preoperative data.

**Table 2**. .Postoperative outcomes between the two groups.

**Table 3.** Details of postoperative complications between the two groups.

**Table 4.** Patient characteristics and outcomes before and after 2008.

**Table 5.** Univariable Logistic Regression: Risk factors for complications and death.

**Table 6.** Multivariable Logistic Regression: Independent predictors for complications and death.

**AUTHOR CONTRIBUTIONS**

The lead statistician was Fotis Polydoros; all other co-authors were members of the Liverpool Pancreas Multidisciplinary Team. All authors contributed to this study in accordance to the International Committee of Medical Journal Editors guidelines and conform to substantive contributions by all of the authors towards the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and approval of the final version. The data quality assurance, analysis, interpretation and writing of the manuscript was initially conducted by Ilias P Gomatos, Fotis Polydorosand John P Neoptolemos. Subsequent amendments and contributions with final approval was made by all of the authors.

**CONFLICTS OF INTEREST**

All of the authors declare that they do not have any conflicts of interest.

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