Pancreatology 22 (2022) 67–73

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Early infection is an independent risk factor for increased mortality in patients with culture-confirmed infected pancreatic necrosis

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ARTICLE INFO

Article history:
Received 23 April 2021
Received in revised form
1 November 2021
Accepted 3 November 2021
Available online 9 November 2021

ABSTRACT

Background: Mortality in infected pancreatic necrosis (IPN) is dynamic over the course of the disease, with type and timing of interventions as well as persistent organ failure being key determinants. The timing of infection onset and how it pertains to mortality is not well defined.
Objectives: To determine the association between mortality and the development of early IPN.
Methods: International multicenter retrospective cohort study of patients with IPN, confirmed by a positive microbial culture from (peri) pancreatic collections. The association between timing of infection onset, timing of interventions and mortality were assessed using Cox regression analyses.

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https://doi.org/10.1016/j.pan.2021.11.003

Keywords:
Infected pancreatic necrosis
Necrosectomy
Mortality
Surgery
Pancreatic necrosis
Necrotizing pancreatitis
Minimally invasive surgery

Results: A total of 743 patients from 19 centers across 3 continents with culture-confirmed IPN from 2000 to 2016 were evaluated, mortality rate was 20.9% (155/734). Early infection was associated with a higher mortality, when early infection occurred within the first 4 weeks from presentation with acute pancreatitis. After adjusting for comorbidity, advanced age, organ failure, enteral nutrition and parenteral nutrition, early infection (≤4 weeks) and early open surgery (≤4 weeks) were associated with increased mortality [HR: 2.45 (95% CI: 1.63–3.67), $p < 0.001$ and HR: 4.88 (95% CI: 1.70–13.98), $p = 0.003$, respectively]. There was no association between late open surgery, early or late minimally invasive surgery, early or late percutaneous drainage with mortality ($p > 0.05$).
Conclusion: Early infection was associated with increased mortality, independent of interventions. Early surgery remains a strong predictor of excess mortality.

1. Introduction

Infected pancreatic necrosis (IPN) is one of the most serious complications of acute pancreatitis (AP), being one of the main drivers of mortality in this disease [1]. Despite significant advances in management, the associated mortality remains at approximately 15–20% [2,3].

Most studies evaluating outcomes in patients with IPN have not adjusted for either the timeframe when infection developed and/or the timing of therapeutic interventions. In addition, they have included mixed cohorts of patients with sterile, presumed infected and proven infected pancreatic necrosis. One of the earliest observations indicating the dynamic nature of mortality over time in acute necrotizing pancreatitis (ANP) was that delaying open surgery improved survival. This led to the development and subsequent widespread adoption of the step up approach for the management of pancreatic necrosis. The early diagnosis of IPN is collinear to early intervention, as the presence of infection triggers intervention. There is limited data linking early infection to poor clinical outcomes [4]. Additionally, the time point where early diagnosis of infection influences clinical outcomes has not been clearly elucidated.

The aim of this study was to determine the association between mortality and the development of early IPN, in a large multicenter cohort of patients with culture confirmed IPN.

2. Methods

2.1. Study design, population and data collection

This was a multicenter retrospective cohort study with 19 tertiary referral centers, 6 in North America, 11 in Europe and 2 in Asia. Patients meeting criteria for inclusion between 2000 and 2016 were identified from each center using hospital registries and databases. *Consecutive patients were enrolled at each center where possible. Not all centers enrolled patients over the entire 16-year period of the study.* Data were collected according to a predefined clinical research form. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval from the institutional review board at the principals investigators center, Johns Hopkins Hospital on November 25th, 2015. The study was also approved by the relevant local ethical committee at each center. Consent by the patient or their health care advocate was not required for enrollment as this was a retrospective study posing minimal risk to the patient.

The study was approved by the Institutional Review Board of each centers and complied with Health insurance Portability and Accountability Act (HIPPA) regulations.

Data for a proportion of patients included in this study, has been previously included in single center studies on infected and sterile necrosis [5–7].

2.2. Inclusion criteria

Patients were required to meet all four of the following inclusion criteria: 1) age ≥18 years; 2) AP, defined according to the revised Atlanta classification, 2012; 3) Parenchymal acute necrotizing pancreatitis (ANP), defined as either lack of enhancement of pancreatic parenchyma on contrast enhanced CT or contrast enhanced MRI abdomen and 4) IPN, defined as a positive microbial culture for any organism obtained from the pancreatic bed through radiology, endoscopy and/or surgery at any time during the course of disease [5,8].

2.3. Definitions of variables

Inpatient mortality was defined as death occurring during hospitalization with AP.

Date of diagnosis of IPN was defined as the number of days from initial presentation with AP to the date the first positive culture was acquired from the (peri) pancreatic bed.

Date of: open surgery, minimally invasive surgery and percutaneous drain was defined as the number of days from initial presentation with AP to open surgical necrosectomy, minimally invasive surgery and percutaneous drain, respectively.

Minimally invasive surgery was defined as: video assisted retroperitoneal debridement (VARD), percutaneous endoscopic necrosectomy/lavage (PEN) and minimal access retroperitoneal pancreatic necrosectomy (MARPN) [7,9,10]. Early minimal invasive surgery was defined as surgery within 30 days from presentation with AP. Endoscopic interventions were defined as endoscopic transmural drainage and/or debridement of the IPN cavity.

Comorbidity was calculated on presentation using the Charlson cormorbidity index (CCI) [11].

Organ failure was defined according to the revised Atlanta classification [8]. Transient organ failure (TOF) was defined as organ failure lasting for <48 h and persistent organ failure (POF) was defined as organ failure lasting for ≥48 h. If the duration of organ failure could not be clearly defined it was labeled as unknown duration of organ failure (UDOF).

The use of enteral and parenteral nutrition was obtained before and after the diagnosis of IPN.

3. Statistical analysis

Continuous and categorical data were compared between groups using standard parametric and non-parametric tests. Time to event analysis was conducted using the Kaplan-Meier method with log rank test. Censoring was performed at discharge with AP. Multivariable Cox regression analysis was performed to evaluate

the variables associated with mortality. In development of the multivariable regression models, the continuous variables: age and CCI were examined with Lowess plots to help determine the best fit for these variables [12]. These variables were evaluated as both continuous variables with and without linear and/or cubic spline terms and as multiple different categorical variables to determine the best fit for each continuous variable in the Cox models. If there was no difference in the fit of a variable using categorical terms as compared to spline terms, the categorical variable was chosen for simplicity of interpretation. Cox proportional assumptions were checked using Schoenfeld residuals. Multilevel survival models were used to adjust for any variation seen across different centers. Missing data was reconciled retrospectively with the specific center(s). The results are presented as estimated hazards ratio (HR) with respective 95% confidence intervals (95% CI) and *p* values. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA version 16 (College Station, TX, U.S.A.).

4. Results

After excluding 44 patients for a lack of a positive (peri) pancreatic culture or missing data, the final cohort included 743 patients with confirmed IPN. The number of patients enrolled per center over a given time period is described in supplemental results. The demographic and clinical characteristics of the cohort are described in Table 1. Patients who died during hospitalization were older, had a higher burden of comorbid diseases and were more likely to have undergone early surgery ($p < 0.001$). The median (IQR) number of days from admission to a diagnosis of IPN was 27 (15–44). Fig. 1 displays a histogram showing the time of IPN diagnosis across our patient cohort. There were 155 (20.9%) inpatient deaths during the first 365 days from presentation. The median (IQR) time from admission to death was 61 (33–87) days. The timing of inpatient death across our patient cohort is shown as a histogram in Fig. 2.

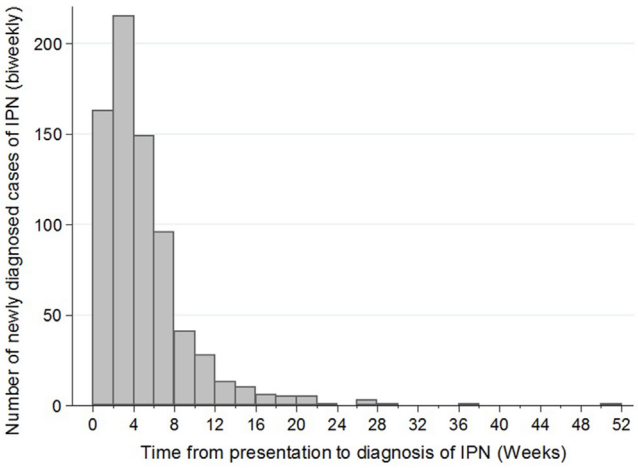

Fig. 1. Timing for the Diagnosis of Infected Pancreatic Necrosis. A histogram demonstrating the time from initial presentation (weeks) to the diagnosis of infected pancreatic necrosis, defined as the time at which the first positive culture from the (peri) pancreatic bed was obtained.

4.1. Relationship between age, comorbidity and organ failure on mortality

Advancing age, increased CCI index and the presence of any type of were all associated with mortality on a univariable and multivariable cox regression, these results are presented in Table 2. There were no significant interaction terms between these variables.

4.2. Relationship between mortality and timing of: open necrosectomy, minimally invasive surgery, percutaneous drain placement and nutrition

Open necrosectomy was associated with increased mortality on univariable analysis (HR [95%CI]: 1.95 [1.41–2.70], $p < 0.001$). Day

Table 1
Demographic and clinical details of cohort.

Variable	Total patients	Survivors	Nonsurvivors	P
	n (%, SD or IQR)	n (%, SD or IQR)	n (%, SD or IQR)	
	743	588 (79.1%)	155 (20.9%)	
Age				
- < 60	430 (57.9)	377 (64.1)	53 (34.2)	<0.001
- ≥ 60 and <70	172 (23.2)	124 (21.1)	48 (31)	0.014
- ≥ 70	141 (19)	87 (14.8)	54 (34.8)	<0.001
Male Sex	517 (69.6)	408 (69.4)	109 (70.3)	0.845
Charleson comorbidity index (CCI) score				
- CCI 1	246 (74.0)	214 (81.1)	32 (47.2)	<0.001
- CCI 2 to 3	122 (16.4)	83 (14.1)	39 (25.2)	0.001
- CCI ≥4	71 (9.6)	28 (4.8)	43 (27.7)	<0.001
Etiology				
- Biliary	287 (48.8)	75 (48.4)	362 (48.7)	0.122
- Alcohol	167 (22.5)	140 (23.8)	27 (17.4)	
- Other	214 (28.8)	161 (27.4)	53 (34.2)	
Transferred from Outside Hospitals	466 (62.7)	374 (63.6)	92 (59.4)	0.351
Early diagnosis of IPN (≤ 4 Weeks)	376 (57.7)	283 (48)	95 (61.3)	0.004
Interventions				
- Surgical Necrosectomy	356 (48)	255 (43.4)	101 (65.2)	<0.001
- Minimally invasive surgery	251 (33.8)	212 (36.1)	39 (25.1)	0.013
- Endoscopic therapy	59 (7.9)	53 (9)	6 (3.9)	0.043
- Percutaneous drain	361 (48.6)	287 (48.8)	74 (47.7)	0.857
Organ failure				
- Transient organ failure	92 (12.4)	63 (10.7)	29 (18.7)	0.009
- Persistent organ failure	240 (32.3)	154 (26.2)	86 (55.5)	<0.001
- Unknown duration of organ failure	76 (10.2)	55 (9.4)	21 (13.5)	0.136

CCI: Charleson comorbidity index; IPN: Infected pancreatic necrosis; IQR: Interquartile range; SD: Standard deviation.

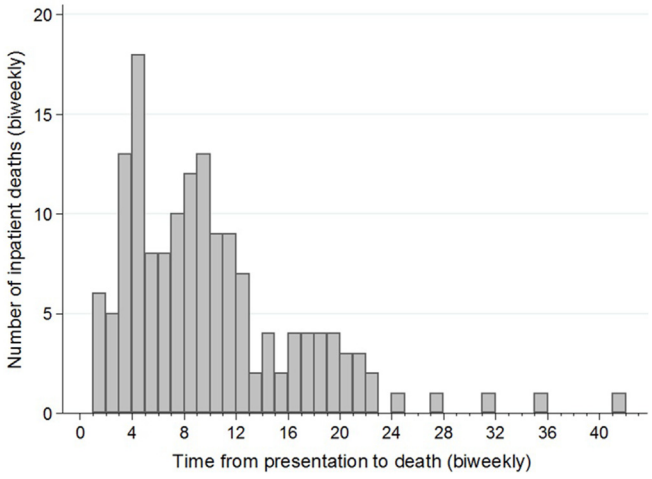

Fig. 2. Timing of Mortality in Infected Pancreatic Necrosis. A histogram demonstrating the time from initial presentation (weeks) to inpatient mortality.

from first presentation with acute pancreatitis to open surgery was associated with a reduction in mortality on univariable analysis (Per one-day increase from presentation to open necrosectomy: HR [95% CI]: 0.99 [0.98–0.99], p = 0.028).

In a similar fashion to the evaluation of early diagnosis, time to open necrosectomy was evaluated in 2 week intervals. As there was no difference in mortality between patients who underwent an open necrosectomy from week 1–2 as compared to week 3–4 (p = 0.81), the first 4 weeks of time to open necrosectomy was combined into a single group, termed, early open necrosectomy. As there was no difference in mortality for patients who underwent an open necrosectomy during any 2-week time interval from 4 weeks onward, patients who were underwent an open necrosectomy after 4 weeks were combined into a single group (p = 0.98), termed, late open necrosectomy. Patients with early open necrosectomy had a higher mortality than both patients who had a late open necrosectomy and those patients who did not have an open necrosectomy (HR [95%CI]: 0.51 [95% CI: 0.33–0.78], p < 0.001 and 0.34 [95% CI: 0.22–0.53], p < 0.001, respectively) and multivariable cox models necrosectomy (HR [95%CI]: 0.22 [95% CI: 0.08–0.60], p = 0.003 and 0.19 [95% CI: 0.07–0.54], p = 0.002, respectively). Patients who underwent late open necrosectomy had a higher mortality than patients who did not undergo an open necrosectomy on univariate but not multivariable analysis (HR (95%CI): 0.67 [95% CI: 0.45–0.98], p = 0.041 and 0.81 [95% CI: 0.54–1.23], p = 0.329).

Minimally invasive surgery was associated with mortality on univariable but not multivariable analysis [HR (95%CI): 0.38 (0.24–0.61), p < 0.001 and 0.79 (0.45–1.38), p = 0.414, respectively]. Day from first presentation with acute pancreatitis to minimally invasive surgery was associated with a reduction in mortality on univariable but not multivariable analysis [Per one-day increase from presentation to minimally invasive surgery: HR (95% CI): 0.97 (0.95–0.99), p = 0.007 and 0.99 (0.97–1.01), p = 0.335, respectively]. In a similar fashion to both early diagnosis and early surgery, minimally invasive surgery was evaluated as early minimally invasive surgery (≤28 days) or late minimally invasive surgery (>28 days). Early minimally invasive surgery was associated with a reduction in mortality on univariable but not multivariable analysis (HR [95%CI]: 0.27 [0.05–0.49], p < 0.001 and 0.69 [0.36–1.4], p = 0.27a, respectively). Late minimally invasive surgery was not associated with mortality on univariable or

Table 2
Cox model for interventions and inpatient mortality.

	Univariable analysis		Multivariable analysis model *	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Age, years				
- < 60	1.00		1	
- ≥ 60 and <70	2.99 (1.93–4.62)	<0.001	1.67 (1.03–2.7)	0.037
- ≥ 70	4.94 (3.17–7.7)	<0.001	2.27 (1.38–3.72)	0.001
Charleson comorbidity index (CCI) score				
- CCI ≤1	1.000		1	
- CCI 2 to 3	2.74 (1.84–4.09)	<0.001	1.66 (1.05–2.62)	0.029
- CCI ≥4	6.5 (4.19–10.01)	<0.001	3.79 (2.29–6.28)	<0.001
Organ failure				
- None	1		1	
- Transient	8.51 (4.26–17.01)	<0.001	5.99 (2.89–12.44)	<0.001
- Persistent	14.4 (7.8–26.61)	<0.001	9.86 (5.33–18.22)	<0.001
- Unknown duration	4.17 (2.14–8.12)	<0.001	3.57 (1.8–7.11)	<0.001
Nutrition				
- Enteral nutrition	0.37 (0.24–0.56)	<0.001	0.38 (0.24–0.59)	<0.001
- Parenteral nutrition	1.25 (0.83–1.90)	0.285	1.40 (0.92–2.14)	0.114
Early IPN (≤ 4 weeks)	2.43 (1.73–3.42)	<0.001	2.45 (1.63–3.67)	<0.001
Interventions				
- Open necrosectomy				
Early (≤4 weeks)	2.94 (1.87–4.61)	<0.001	4.88 (1.70–13.98)	0.003
Late (>4 weeks)	1.5 (1.02–2.2)	0.410	1.23 (0.81–1.87)	0.329
- Minimally invasive surgery				
Early (≤4 weeks)	0.28 (0.15–0.5)	<0.001	0.69 (0.36–1.34)	0.274
Late (>4 weeks)	0.62 (0.34–1.14)	0.124	0.94 (0.47–1.88)	0.867
- Percutaneous drain placement				
Early (≤4 weeks)	0.44 (0.27–0.73)	0.002	0.91 (0.52–1.57)	0.724
Late (>4 weeks)	1.04 (0.67–1.62)	0.85	1.03 (0.62–1.72)	0.91
- Endoscopic drainage/debridement	0.37 (0.15–0.92)	0.032	–	–

* Multilevel data analysis was performed based on center on the univariable and multivariable cox model.
** The multivariable model was adjusted for age, CCI, organ failure, enteral nutrition, parenteral nutrition, early IPN, open necrosectomy (early and late) and the variable of interest.
CCI: Charleson comorbidity index; CI: Confidence interval; HR: Hazard ratio.

multivariable analysis (HR [95%CI]: 0.62 [0.34–1.14], p = 0.124 and 0.94 [0.47–1.89], p = 0.867, respectively).

Percutaneous drain placement was not associated with mortality on univariable or multivariable analysis (HR [95%CI]: 0.69 [0.47–1.02], p = 0.063 and 0.97 [0.62–1.51], p = 0.9, respectively). Day of percutaneous drain placement was associated with mortality on univariable but not multivariable analysis (HR [95%CI]: 0.98 [0.97–0.99], p = 0.006 and 0.99 [0.98–0.1.01], p = 0.417, respectively). In a similar fashion to early diagnosis, early surgery and early minimally invasive surgery, percutaneous drain placement was evaluated as early percutaneous drain placement (≤28 days) and late percutaneous drain placement (>28 days). Early percutaneous drain placement was associated with mortality on univariable but not multivariable analysis (HR [95%CI]: 0.44 [0.27–0.73], p = 0.002 and 0.90 [0.52–1.57], p = 0.724, respectively). Late percutaneous drain placement was not associated with mortality on univariable or multivariable analysis (HR [95%CI]: 1.04 [0.67–1.62], p = 0.85 and 1.03 [0.62–1.72], p = 0.91, respectively).

Endoscopic transmural drainage was associated with a lower mortality on univariable analysis (HR [95%CI]: 0.37 [0.15–0.92], p = 0.032). It was elected not to include endoscopic transmural drainage as a variable in the final multivariable models since only 7.9% of the total cohort underwent this approach. There was a very low mortality rate in this group with only 6 inpatient deaths. No patient in the cohort was managed with aspiration and culture alone. All patient received either: percutaneous drain, open necrosectomy, minimal invasive surgery and/or endoscopic necrosectomy.

Enteral nutrition during hospitalization was associated with a reduction in mortality on both univariable and multivariable analysis (HR [95%CI]: 0.36 [0.24–0.56], p < 0.001 and 0.38 [0.24–0.59], p < 0.001, respectively). Parenteral nutrition was not associated with mortality on univariable or multivariable analysis (HR [95%CI]: 1.25 [0.83–1.90], p = 0.285 and 0.1.40 [0.92–2.14], p = 0.114, respectively).

All multivariable Cox analysis were adjusted for age, CCI, organ failure, early diagnosis, early surgery, enteral and parenteral nutrition, as these variables were found to be significant on both the univariable and multivariable analysis.

4.3. Relationship between time of diagnosis, mortality and persistent organ failure

Day of IPN diagnosis from initial presentation was associated with a reduction in mortality [Per one-day from presentation to diagnosis, HR (95% CI): 0.985 (0.979–0.993), P < 0.001]. Time to diagnosis of IPN was evaluated in 2 week intervals. As there was no difference in mortality between patients diagnosed with IPN from week 1–2 as compared to those diagnosed from week 3–4 (p = 0.74), the first 4 weeks of time to diagnosis was combined into a single time period, termed, early diagnosis. As there was no difference in mortality for patients diagnosed with IPN during any 2-week time interval from 4 weeks onward, patients who were diagnosed after 4 weeks were combined into a single group (p = 0.59), termed, late diagnosis. Patients with early diagnosis had a higher mortality that patients with late diagnosis on a univariable multilevel and multivariable analysis (HR [95%CI]: 2.43 [95% CI: 1.73–3.42], p < 0.001 and 2.45 [95% CI: 1.63–3.67], p < 0.001), Table 2 and Fig. 3. Early diagnosis was associated with the presence of POF on univariable and multivariable logistic regression analysis (HR [95%CI]: 1.38 [95% CI: 1.01–1.87], p = 0.043 and 1.38 [95% CI: 1.01–1.89], p = 0.043), after adjusting for age and CCI.

4.4. Subgroup analysis of the effect of early diagnosis on patients who did not undergo open necrosectomy

A sensitivity analysis was performed to evaluate the independent effect of the timing of diagnosis in patients who did not have an open necrosectomy. A total of 397 patients did not undergo open necrosectomy. Early infection (≤28 days) was associated with increased mortality on univariable and multivariable analysis (HR [95%CI]: 3.24 [1.83–5.73], p < 0.001 and 2.43 [1.31–4.50], p = 0.005, respectively), after adjusting for age, CCI, organ failure, parenteral nutrition and enteral nutrition administration.

5. Discussion

There are a number of notable findings from this study of patients with culture-confirmed IPN. First, early infection is associated with a more fulminant disease, as indicated by a higher incidence of POF and mortality. Approximately half of the present cohort (50.8%) developed early infection, making early infection of critically importance to major clinical outcomes. Second, early open surgery is a clear determinant of mortality, while interventions such as minimally invasive surgery or percutaneous drains do not appear to affect mortality, regardless of timing.

In early acute pancreatitis, activation and persistence of the inflammatory cascade, clinically manifested as SIRS and can progress to organ failure [13]. Superinfection of the necrotic (peri) pancreatic tissue at this early stage is likely to exacerbate the

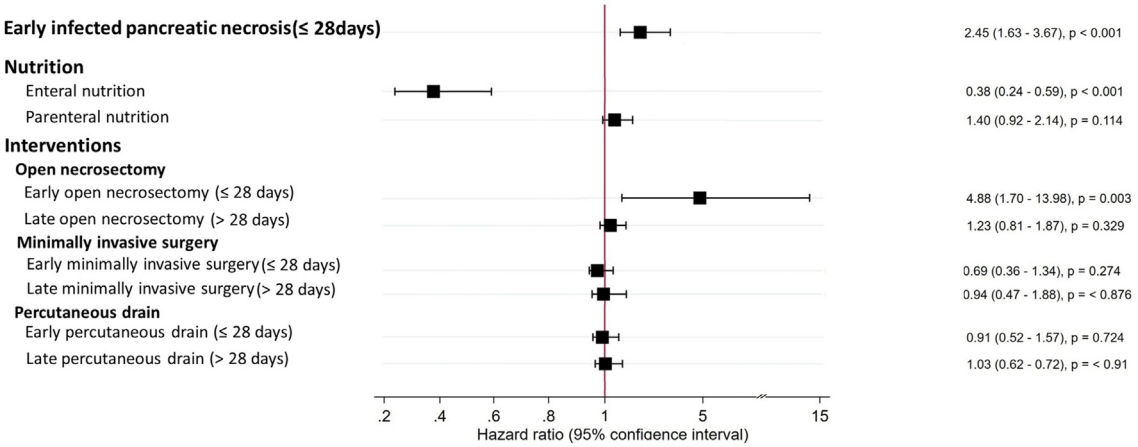

Fig. 3. Impact of Timing of Diagnosis, Nutrition and Timing of Interventions on Mortality in Infected Pancreatic Necrosis. Forest plot of the multivariable Cox model for inpatient mortality. The results of this Forest plot are derived from the multivariable model in Table 2.

inflammatory status of the patients leading to poorer clinical outcomes, especially in those who have already developed organ failure. There are a number of important questions generated from the concept of early infection and its association with clinical outcomes. Secondary infection of (peri) pancreatic tissue after surgical or endoscopic interventions is commonly observed in patients with presumed sterile (peri) pancreatic necrosis [14]. Delaying these interventions in patients who do not have suspected or confirmed IPN will avoid the risk of converting early sterile into early infected necrosis. Randomized controlled trials that have shown endoscopic transmural drainage/debridement to be superior to percutaneous minimally invasive surgery using composite end points but these have not evaluated how timing of infection influences outcomes [15–17]. It is possible that patients with early infection benefit the most from an endoscopic transmural drainage approach as this is associated with a reduction in inflammatory cytokines as compared to minimally invasive surgery [17]. In patients who develop late infection, following recovering from the acute inflammatory changes of early acute pancreatitis and who have more mature collections, the difference between a minimally invasive surgical and endoscopic transmural approach may not be as apparent and end points focused on cost and treatment burden may be more relevant. The difference in major clinical outcomes seen in early and late infection in part explains the use of composite endpoints in comparative randomized controlled trials in this field, as mortality and organ failure are less common in patients with late infection who are the target cohort for many of these interventions. Composite end points with additional outcomes that have a lower impact on patient's clinical course are; therefore, required to generate sufficient power for these studies. Future studies that stratify patients with IPN into early and late infection will help to enhance our understanding of the relationship between early infections and outcomes. Referral bias may have resulted in under or overestimation of the overall prevalence of early infection. Regardless, this data highlights that early infection is an important determinant of mortality and appropriate measures should be taken when early infection is suspected, especially in patients not responding to supportive care.

The historical rationale for early open surgery in patient with IPN was to gain source control and consequentially reverse organ failure [18]. There are two problems with early open surgery. The first is that it delivers a "second hit" with extreme pathophysiological stress with amplification of the pre-existing systemic inflammatory response syndrome. The second problem is that despite infection, liquefaction of the affected areas of the pancreas and surrounding fat has not yet become encapsulated, thus requiring major partial pancreatectomy to remove diseased tissues. Under such circumstances, the risk of uncontrollable hemorrhage and subsequent death is extremely high. Delaying surgery for the establishment of "walled-off" necrosis greatly simplifies necrosectomy and helps to balance the deleterious "second hit" associated with open surgery. Initial data on the use of CT-guided percutaneous drainage catheters, highlighted that nearly half of all patients with infected necrosis could avoid early surgery by using these catheters to control sepsis [19]. This observation was key in changing the paradigm for managing IPN as delaying surgery resulted in a marked reduction in mortality [20]. This has led to the development of the 'step-up' approach, where initial interventions are selected from minimally invasive methods such as percutaneous drains, endoscopic transmural drainage, followed by additional methods to remove the necrosis such as video assisted open necrosectomy (VARD) at a subsequent time point. The 'step-up' approach was shown to be associated with a significant reduction in a composite outcome that consisted of mortality and new onset multiorgan failure in a landmark multicenter randomized controlled trial from the Netherlands employing percutaneous radiological placed drains followed by VARD if required [2]. Minimal access retroperitoneal pancreatic necrosectomy (MARPN, or skunking) actually combines both procedures without the need for open necrosectomy [7]. Open surgery is then only required for inaccessible collections or serious complications such as colonic necrosis or fistulae. A multicenter, multinational propensity matched cohort study in a mixed cohort of patients with sterile and infected pancreatic necrosis also reported a higher mortality in patients undergoing open surgery as compared to minimally invasive surgery and endoscopic transmural drainage [21]. The importance of the timing of intervention was not addressed in this study [21]. In addition to a reduction in mortality, minimally invasive surgery and endoscopic transmural drainage were associated with a lower rate of complications and post procedural organ failure [7,17].

A limitation of this study is that the time for the diagnosis of IPN was defined as the time the first positive culture was obtained. It is possible that a patient may have had clinical evidence of infection prior to obtaining a pancreatic culture. The use of this definition, however, removes any ambiguity associated with using a "clinical suspicion" for both the diagnosis itself and the time of diagnosis of IPN, variables that are not reliably obtained in retrospective studies. Due to the small number of patients who underwent endoscopic transmural drainage, this technique could not be robustly evaluated in the multivariable model. However, minimally invasive surgery has been more robustly evaluated and has been comparable to endoscopic transmural drainage in several randomized controlled trials [15,16]. OF is known to be the strongest predictor of mortality in patients with acute pancreatitis, a finding validated in this study. The timing of the development of was not accounted for in this study. While the authors acknowledge that patients who undergo open necrosectomy with concomitant organ failure may have different outcomes in comparison to patients who underwent open necrosectomy without concomitant organ failure, minimally invasive techniques have been associated with a reduction in mortality in a propensity matched study accounting for the severity of AP at the time of intervention [21]. The Dutch acute pancreatitis study group found no difference in mortality based either on the time at which organ failure occurred or the duration of organ failure [22]. Different centers had a different rate of enrollment over different periods of the study which introduces the possibly of a selection bias. In the multivariable models each center was accounted for, controlling, to some degree for this potential bias. "The reasons for differing rates of patient accrual and different years to start and end time for patient accrual is multifactorial. Centers were limited to starting data collection based on their individual ability to search medical records for inclusion criteria. A number of centers had acquired the data set for their center as part of previously published cohort studies, listed in the methods section. Finally, it is assumed that referral patterns differ across individual centers and across different countries, such that the number of newly diagnosed cases of infected necrosis would have significant variation across each center in the study." There are several strengths of the present study. The inclusion of patients with IPN confirmed by culture ensured homogeneity in the clinical diagnosis since many prior studies looking at intervention looked at both infected and non-infected pancreatic necrosis, which are associated with different mortality rates. As a multinational study, the patient cohort is heterogeneous, allowing our findings to be more generalizable. The majority of studies in the acute pancreatitis literature to date have not used time to event analysis. The use of time to event analysis as compared to standard logistic regression is more powerful, allowing for censoring and is commonly used in epidemiological studies of major diseases outcomes. Finally, this study used a vigorously

generated mortality model that included both age and comorbidity as important covariates in determining mortality [12,23].

In conclusion, the dynamic nature of IPN has further been defined in this study. Early infection, independent of timing or type of intervention is associated with mortality. To further personalize care for this disease, future studies should incorporate early infection as a key outcome variable so that we may better understand the nuances of managing this disease.

Financial support

No direct financial support was obtained for this study.

Declaration of competing interest

Mouen Khashab is a consultant for Boston Scientific, Olympus and Medtronic. Robert A. Moran is a consultant for Cook medical. Vikesh K Singh is a consultant to Abbvie and Theraly, advisory board participant for Cook Medical, and receives grant funding from Orgenesis. Tyler Stevens is a consultant for Boston Scientific. All other authors have no conflicts of interest to disclose.

Acknowledgement

The work conducted by centers in Hungary was supported by a Momentum Grant from the Hungarian Academy of Sciences (LP2014-10/2014 to PH). We are grateful to Erika Darvasi (Szeged, Hungary)) who provided administrative support for the data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.11.003.

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