World J Surg (2019) 43:929–936
https://doi.org/10.1007/s00268-018-4842-0

ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Intraoperative Fluid Administration and Surgical Outcomes Following Pancreaticoduodenectomy: External Validation at a Tertiary Referral Center

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Published online: 30 October 2018

Abstract

Background While intraoperative fluid overload is associated with higher complication rates following surgery, data for pancreaticoduodenectomy are scarce and heterogeneous. We evaluated multiple prior definitions of restrictive and liberal fluid regimens and analyzed whether these affected surgical outcomes at our tertiary referral center.

Methods Studies evaluating different intraoperative fluid regimens on outcomes after pancreatic resections were retrieved. After application of all prior definitions of restrictive and liberal fluid regimens to our patient cohort, relative risks of each outcome were calculated using all reported infusion regimens.

Results Five hundred and seven pancreaticoduodenectomies were included. Nine different fluid regimens were evaluated. Two regimens utilized absolute volume cutoffs, and the remaining evaluated various infusion rates, ranging from 5 to 15 mL/kg/h. Total volume administration of >5000 mL and >6000 mL was associated with increased complications (RR 1.25 and RR 1.17, respectively) and >6000 mL with increased sepsis (RR 2.14). Conversely, a rate of <5 mL/kg/h was associated with increased risk of postoperative pancreatic fistula (POPF, RR 3.16) and sepsis (RR 3.20), <6.8 mL/kg/h with increased major morbidity (RR 1.64) and sepsis (RR 2.27), and <8.2 mL/kg/h with increased POPF (RR 2.16). No effects were observed on pulmonary complications, surgical site infections, length of stay, or mortality.

Conclusions In an uncontrolled setting with no standard intraoperative or postoperative care map, the volume of intraoperative fluid administration appears to have limited impact on early postoperative outcomes following pancreaticoduodenectomy, with adverse outcomes only seen at extreme values.

Introduction

Pancreatic surgery is associated with significant morbidity following resection. Reduction of morbidity has been a major primary goal of clinical investigation. Although hospital length of stay (LOS) and mortality have improved, the rate of complications after pancreaticoduodenectomy

The paper was presented during the Digestive Disease Week® (DDW) at the Walter E. Washington Convention Center in Washington, D.C., June 2–5, 2018.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-018-4842-0) contains supplementary material, which is available to authorized users.

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(PD) has remained high, owing to the technical complexity of the operative intervention [1, 2].

In recent years, multimodal enhanced recovery approaches have been proposed and implemented to minimize the surgical stress response, by providing a physiologic perioperative milieu for enhanced recovery. Such approaches have been reliably validated following colorectal resection, and have since been broadly extrapolated, despite limited data, to include other organ resections, including PD [3, 4]. Central to enhanced recovery after surgery (ERAS) pathways has been the notion that finely balanced optimization of intraoperative fluid administration impacts postoperative morbidity and mortality following major surgery. While fluid overload is associated with large fluid shifts, delay in recovery, and worsened outcomes, restrictive fluid regimens may also result in inadequate tissue perfusion, insufficient oxygen delivery, and flow-dependent-organ dysfunction [5]. As such, utilization of such regimens is not without risk. More recently, "goal-directed" fluid therapy and "near-zero" balanced intraoperative fluid administration, which replaces all measured fluid losses without replacement of the loss-to-third space, appears to be associated with decreased postoperative ileus, lower rate of postoperative complications, shorter recovery, and shorter hospital LOS [6–9].

To date, eight retrospective studies [10–17] and five randomized controlled trials [18–22] have evaluated the effects of different intraoperative fluid administration rates during pancreatic surgery on surgical outcomes. These studies were riddled with broad heterogeneity in the definitions for restrictive, or low, and liberal, or high, fluid administration rates, with variable outcomes.

The aim of our study was to retrospectively evaluate all prior reported cutoffs for intraoperative fluid infusion rates using a single cohort of patients undergoing PD at our tertiary referral center, and to retrospectively analyze whether different intraoperative fluid volumes affected surgical outcomes. We hypothesized that given the high underlying morbidity inherently associated with PD, variability in fluid administration was unlikely to significantly impact outcomes. The potential implications of these findings for implementation of ERAS protocols in pancreatic surgery may be significant.

Methods

Literature search

An extended web search was conducted using the MEDLINE, EMBASE, and PubMed databases (June 1966 to December 2017). The search terms used were "pancreaticoduodenectomy" or "pancreatoduodenectomy," and "fluid." The search was limited to the English language and to studies including at least 20 patients. All studies comparing surgical outcomes following pancreatic resections with different intraoperative fluid regimens were considered, and cutoff points defining restrictive, liberal, and/or overload were extracted. Abstracts, case reports, systematic reviews, and meta-analyses were excluded. Reference lists were reviewed to broaden the search.

Data collection

A retrospective data analysis was performed using a prospectively maintained institutional database to identify patients who underwent PD from January 2007 to December 2015 at the Massachusetts General Hospital. Data on type and quantity of fluid administration were manually extracted from the operative records. Demographic data, perioperative variables, and postoperative outcomes were analyzed from institutional prospective databases.

Intraoperative fluid administration included intravenous fluids administered from the induction of general anesthesia until the end of the surgical procedure. Packed red blood cells were transfused when the hemoglobin level was less than 8 g/dL [23]. In keeping with other studies, blood product (packed red blood cells, fresh frozen plasma, or platelet units) was not included in the computation of the intraoperative crystalloid and colloid fluid volumes and infusion rates. Albumin infusion was included in the overall infusion rate.

Perioperative management

All patients were admitted on the same day of their scheduled operation. No patients underwent mechanic bowel preparation. In keeping with institutional protocol, patients were permitted to have a normal meal on the evening before surgery and were encouraged to drink clear liquids up to 2 h before the operation. General anesthesia was administered according to individual anesthesiologist preference. However, an epidural catheter was routinely placed and roughly consistent across the study period. Active monitoring of pressure variation and depth of anesthesia were available, but no standardized algorithm for intraoperative fluid management was applied.

Outcome definition

We analyzed several outcomes including:

1. Overall complications, defined as any 30-day event that resulted in prolongation of hospital LOS, or

required additional interventions during the same, or subsequent, hospitalizations.
2. Major complications, defined as any grade 3 or greater complication per the Clavien-Dindo Classification [24].
3. Postoperative pancreatic fistula (POPF), which were diagnosed and classified according to the most recent International Study Group of Pancreatic Surgery (ISGPS) classification [25].
4. Pulmonary complications, which were analyzed as a composite outcome, and included pneumonia, pleural effusion, and respiratory insufficiency.
5. Sepsis, defined as proven infection with associated systemic inflammatory response syndrome (SIRS).
6. Postoperative mortality, which included deaths up to 90 days following PD.

Statistical analysis

Nine different cutoffs were included and applied to our surgical cohort. For each pair of reported cutoffs (high and low groups), two groups were identified and compared to evaluate the effects of varying fluid regimens on the outcomes listed above. Relative risk (RR) and corresponding 95% confidence intervals (CI) associated with all outcome measures were reported for all previously described regimens.

The Student *t* test and Mann-Whitney *U* test were used to compare parametric and nonparametric continuous variables, respectively. Non-random association for categorical variables was tested with the Fisher's exact test. Statistical significance was assigned at an alpha level of 5%. Calculations were performed with IBM SPSS, version 24 (IBM Corp., Armonk, NY).

Results

Complete records were available for 507 patients who underwent PD at the Massachusetts General Hospital over the predefined 9-year period.

Baseline characteristics are depicted in Table 1. Mean age was 66 ± 13 years, 232 (45.8%) patients were male, and 367 (72.4%) had pancreatic cancer. Patients received a median intraoperative fluid volume of 4250 mL (IQR 3000–5500 mL), with a crystalloid to colloid ratio of 7 to 1. The median infusion rate was 10.2 mL/kg/h (IQR 8.2–13.2 mL/kg/h). To analyze potential changes in the infusion policy over the study period, we divided our population equally into three groups according to the year of operation: 2007 to 2009, 2010 to 2012, and 2013 to 2015. The median infusion rate was consistent over these groups, as shown in Fig. 1 ($p = 0.118$). Similarly, the crystalloid to colloid ratio remained unchanged.

Next, we divided our population into four quartiles, according to intraoperative infusion rates (Table 2). Patients who received higher infusion rates were more likely to be female ($p < 0.001$), had lower body mass indices (BMI) ($p < 0.001$), and experienced more intraoperative bleeding ($p < 0.023$). No differences were observed among the groups with respect to overall morbidity, major complications, POPF rates, pulmonary complications, sepsis, or mortality. This was also the case when the overall amount of fluid infused was evaluated (Supplementary Table 1).

We then evaluated the definitions described by previous studies, comparing standard versus overload, restricted versus overload, or restricted versus standard intraoperative fluid administration regimens. Two studies [12, 13] divided their population into quartiles of overall intraoperative fluid administration and used two regimens for total volume cutoffs, including < 4000 mL versus ≥5000 mL, and < 6000 mL versus >6000 mL [15, 17]. The remaining six regimens evaluated infusion rates ranging between 5 and 15 mL/kg/h [14–16, 18–22].

The definitions and cutoffs described are combined and summarized in Table 3. The regimens reported were broad and heterogeneous. Whereas certain infusion rates may have been considered as restrictive regimens by some groups, others may have defined the same rate as their high volume or control comparator. For example, 10 mL/kg/h was considered as restrictive in one study [19] and conventional in another [20].

The relative risks (RR) and 95% CI's for each outcome (overall morbidity, major complications, POPF, pulmonary complications, sepsis, and mortality) were calculated at all reported cutoffs and are shown in Fig. 2. Intraoperative fluid administration was associated with a significantly increased risk of overall complications only for extremely high total volume cutoffs [RR = 1.25 (1.09–1.44) for total volume >6000 mL, and RR = 1.17 (1.01–1.35) for total volume ≥5000 mL]. Similarly, overall fluid volume of more than 6000 mL was associated with a significantly higher risk of sepsis [RR = 2.14 (1.04–4.42)]. On the other hand, an increased risk of major complications and sepsis was observed for patients who received less than 6.8 mL/kg/h of intraoperative fluid [RR = 1.64 (1.01–2.68) and RR = 2.27 (1.02–5.07), respectively], while infusion rates below cutoffs of 8.2 mL/kg/h and 6 mL/kg/h were associated with higher risk of POPF [RR = 2.16 (1.08–4.32) and RR = 3.16 (1.06–9.41), respectively]. There were no other statistically significant differences noted between the nine different fluid regimens on any of the outcomes described.

Table 1 Baseline demographics of included patients (n = 507)

	Mean ± SD, n (%)	Median (IQR)
Age	66 ± 13	
Gender male	232 (45.8)	
Diabetes mellitus	80 (15.8)	
Body mass index	27.0 ± 5.4	
ASA ≥ 3	194 (38.3)	
Total volume infused (mL)	4433 ± 1819	4250 (3000–5500)
Crystalloid (mL)	3617 ± 1501	3500 (2500–4500)
Colloid (mL)	588±524	500 (0–1000)
Packed red blood cell (n of patients)	95 (18.7)	
Fresh frozen plasma (n of patients)	39 (7.7)	
Albumin (n of patients, mL)	160 (31.6), 228 ± 401	0 (0–500)
Fluid infusion rate (mL/kg/h)	11.0 ± 4.2	10.2 (8.2–13.2)
Estimated blood loss (mL)	719±562	530 (350–950)
Operative time (min)	336±98	

ASA American Society of Anesthesiologists

Discussion

In a single cohort using an institutional prospectively maintained database, we evaluated the effects of prior published *high* and *low* volume intraoperative fluid administration definitions on surgical outcomes following PD. In contrast to prior published data that suggested an increased rate of morbidity following PD in patients who received excess intraoperative fluids [10, 14, 16, 17, 19, 22], we noted that variable fluid interventions had few effects on several outcomes, including overall morbidity, major complications, POPF, pulmonary complications, sepsis, and 90-day postoperative mortality. It was only at extremes of low and high fluid infusion regimens that few associations with major complications, POPF, and sepsis could be identified.

Fluid overload resulting in interstitial edema and local inflammation has been proposed as mechanistic causes of impaired tissue healing, increased risk of postoperative wound complications, and anastomotic leakage in colorectal surgery [6–9, 26]. Additionally, excess fluids have been shown to impair lung function and to increase the risk of pulmonary complications after several elective surgical procedures [27, 28]. Given these findings, achieving a delicate fluid balance has been a critical goal in major elective abdominal surgery during the last decade, with heightened focus for inclusion of more restrictive, goal-directed fluid therapies, among enhanced recovery

Table 2 Population characteristics following division into four quartiles according to intraoperative infusion rates

	<8.2 mL/Kg/h n = 132	8.2–10.2 mL/kg/h n = 123	10.2–13.2 mL/kg/h n = 127	≥13.2 mL/kg/h n = 125	p value
Gender male	71 (53.8)	69 (56.1)	49 (38.6)	43 (34.4)	<0.001
Age	67 ± 12	68 ± 11	65 ± 15	65 ± 13	0.197
Diabetes mellitus	21 (15.9)	23 (18.7)	22 (17.3)	14 (11.2)	0.393
Body mass index	29.9 ± 6.6	27.0 ± 4.7	26.2 ± 4.5	24.7 ± 4.1	<0.001
Estimated blood loss (mL)	639 ± 529	730 ± 606	656 ± 464	856 ± 618	0.008
Pancreatic cancer	94 (71.2)	96 (78.0)	91 (71.7)	86 (68.8)	0.407
Overall complications	87 (65.9)	70 (65.9)	79 (62.2)	80 (64.0)	0.448
Major complications	28 (21.2)	13 (10.6)	22 (17.3)	20 (16.0)	0.146
POPF	13 (9.8)	6 (4.9)	5 (3.9)	6 (4.8)	0.172
Pulmonary complications	11 (8.3)	7 (5.7)	12 (9.4)	10 (8.0)	0.734
Sepsis	11 (8.3)	5 (4.1)	6 (4.7)	8 (6.4)	0.472
90-day mortality	3 (2.3)	3 (2.4)	0 (0.0)	1 (0.8)	0.276

POPF postoperative pancreatic fistula

Table 3 Characteristics of comparative studies incorporated for cutoff values

Study (Type)	"Low" cutoff (Description)	"High" cutoff (Description)	Type of fluid	Type of surgery	Findings
Weinberg 2014 (Retrospective; $n = 150$)	<4000 Restrictive	>5000 Liberal	Mixed	PD	Liberal regimen was associated with higher overall complication rate
Melis 2012 (Retrospective; $n = 188$)	<6000 mL –	≥6000 mL –	Crystalloid	PD	No effect
Kulemann 2017 (Retrospective; $n = 553$)	≤6000 mL –	>6000 mL –	Crystalloid	PD	High total volume correlated with increased infections and reinterventions
Eng 2013 (Retrospective; $n = 124$)	<13.95 mL/kg/h –	>13.95 mL/kg/h –	Mixed	PD	High infusion rate associated with increased 30-d mortality and complications
Wang 2014 (Retrospective; $n = 147$)	<8.2 mL/kg/h Low volume	≥8.2 mL/kg/h High volume	Mixed	PD	High fluid volume was associated with an increased incidence of POPF
Lavu 2013 (RCT; $n = 259$)	10 mL/kg/h –	15 mL/kg/h –	Hypertonic saline versus lactated Ringer's	PD	Hypertonic saline was associated with reduced overall complication rate
Van Samkar 2015 (RCT; $n = 54$)	5 mL/kg/h Restricted	10 mL/kg/h Standard	Crystalloid	PD	No effect
Grant 2016 (RCT; $n = 330$)	6 mL/kg/h Restricted	12 mL/kg/h Liberal	Crystalloid	Mixed resections	No effect
Weinberg 2017 (RCT; $n = 52$)	3.2 mL/kg/h Goal-directed	6.8 mL/kg/h Conventional	Crystalloid	PD	Goal-directed fluid therapy associated with reduced complications and postoperative blood transfusions

PD pancreaticoduodenectomy, *RCT* randomized controlled trial, *POPF* postoperative pancreatic fistula

protocols to reduce the likelihood of complications, improve patient recovery, and decrease hospital LOS [29–31]. As such, restrictive regimens, including "near-zero balance" has been generalized and emphasized for all types of operations, included pancreatic resections, by extrapolation [3].

Interestingly, the largest randomized controlled trial by Grant and colleagues [11] recently failed to demonstrate the superiority of a restrictive fluid regimen over a liberal one following PD, in keeping with our retrospective findings. Similar results were also demonstrated in another large randomized controlled trial comparing a moderate restrictive infusion of hypertonic saline versus liberal infusion of balanced crystalloids [19]. Most recently, a large randomized trial by Myles and colleagues [32] showed no protective effect of a restrictive regimen on complications following major abdominal surgery with an increased rate of acute kidney injury seen as a result of fluid restriction. Finally, two recent meta-analyses [33, 34] derived similar conclusions.

It appears from these combined prospective and retrospective findings that other more important factors may be more important determinants of surgical outcomes following PD, where there is an inherently high morbidity rate. For example, POPF is the commonest severe complication following PD [35] and is more likely influenced by active remnant glands that secrete pancreatic juice rich in proteases, which can digest and disrupt the surrounding tissue, thereby leading to anastomotic dehiscence [36]. In addition, intrinsic characteristics of the gland, including pancreatic stiffness, gland texture, and diameter of the main pancreatic duct would seemingly appear to be more important, well-established, predictors of POPF development [37], rather than the amount of intraoperative fluids.

When we examined the effect of variable fluid administration rates on pulmonary complications specifically, we noted that there were no differences identified across all infusion rates and total fluid amounts. This is also in contrast to prior findings suggestive of a protective effect of fluid restriction on perioperative pulmonary complications following PD [14].

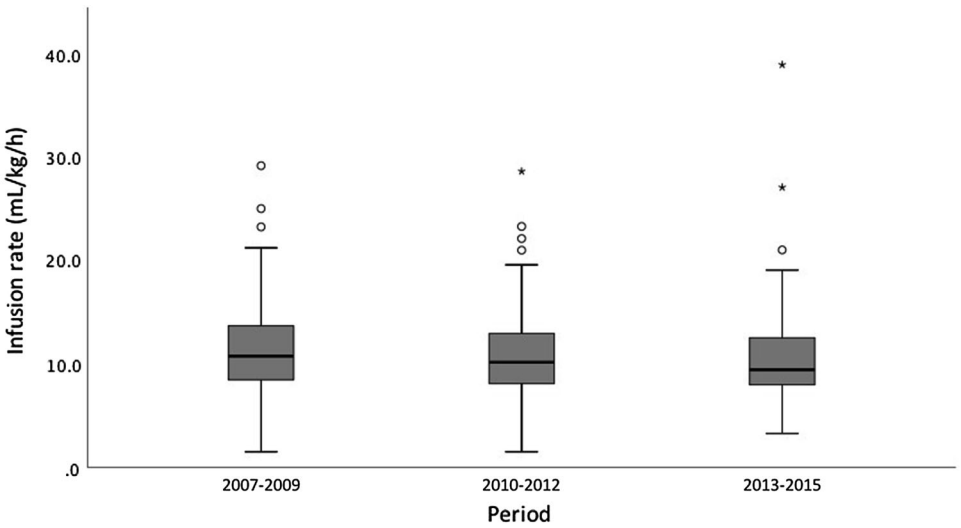

Fig. 1 Median infusion rate over the study period

We observed that very low rates of intraoperative fluid regimens were associated with increased risk of major complications, POPF, and sepsis. These data are consistent with prior observations, suggesting an increased risk of postoperative morbidity associated with hypoperfusion occurring during pancreatic surgery [38]. It appears that, based on the numerous rates examined in our study, both dehydration and overload should be equally avoided, as the relationship between volume of fluid infused during elective surgery and the frequency of postoperative morbidity is "U-shaped" in graphical terms [39]. As such, modalities that can be helpfully utilized to optimize balanced fluid delivery include transesophageal Doppler, lithium dilution, arterial pulse contour analysis, and thoracic bioimpedance [40].

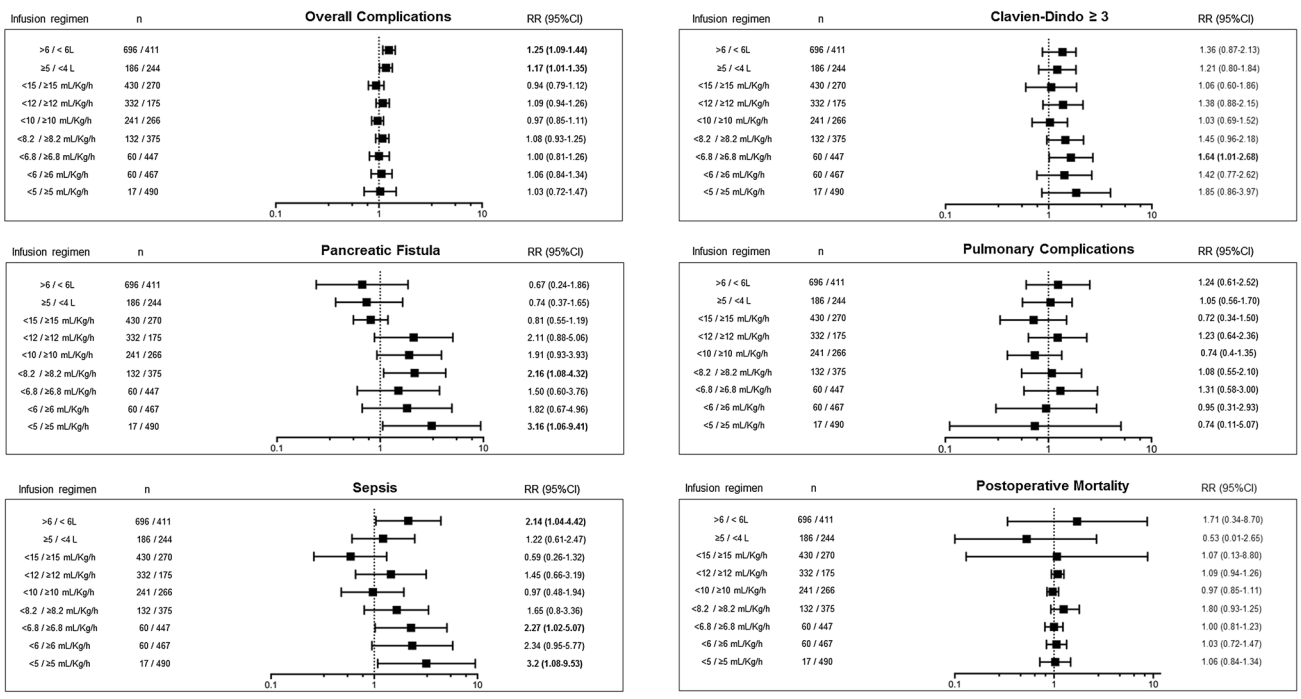

Fig. 2 Effect of different intraoperative infusion regimens on outcomes following pancreaticoduodenectomy. *RR* relative risk, *CI* confidence interval; *n* number of patients

In this study, we also confirmed the remarkable heterogeneity in definitions utilized for low and high volumes of intraoperative fluid administration, which were all applied to our study patient cohort. The absence of standardized definitions is likely responsible for the persistent lack of consensus agreement on perioperative fluid administration during PD [33], but also within the body of literature examining the topic and during trial design.

The present study has some limitations. Given the retrospective design, data on fluid administration in the first days after surgery were not readily available. Since fluid balance in the early postoperative period may also affect surgical outcomes [41], this information may have concealed important differences in the perioperative period, which is interestingly a limitation noted in most previous reports. Importantly, however, five of the nine studies included for validation did not include postoperative fluid administration. Given the retrospective design, no strict management of intraoperative fluid therapy was followed and some uncontrolled confounders related to the anesthesia regimen could have masked potential effects of fluid administration. In addition, intravenous administration of fluids other than colloids and crystalloids was not included within the total administered amount, which is also in keeping with prior reports on this topic. However, we noted that only fewer than 20% of patients received intraoperative packed red blood cell transfusions, 7% received fresh frozen plasma, and 31.6% received albumin for a mean volume of 228 mL only.

In conclusion, our study demonstrates that variable fluid intervention rates outside of extreme highs and lows appear to have limited effects on outcomes following PD. This may be due to the inherently elevated complication rate following PD compared with other major abdominal surgical procedures. Current recommendations for restrictive fluid administration and incorporation into enhanced recovery protocols require further validation following pancreatic resection, given the overall limited effect seen on morbidity and mortality.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interests to disclose.

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