Postoperative long-term outcomes of acute normovolemic hemodilution in pancreatic cancer: A propensity score matching analysis

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Abstract. Acute normovolemic hemodilution (ANH) is a useful intraoperative blood conservation technique. However, the impact on long-term outcomes in pancreatic ductal adenocarcinoma (PDAC) remains unclear. The present study investigated the impact of ANH on long-term outcomes in patients with PDAC undergoing radical surgery. Data from 155 resectable PDAC cases were collected. Patients were categorized according to whether or not they had received intraoperative allogeneic blood transfusion (ABT) or ANH. Postoperative complications, recurrence-free survival (RFS) and disease-specific survival (DSS), before and after propensity score matching (PSM), were compared among patients who did and did not receive ANH. A total of 44 patients (28.4%) were included in the ANH group and 30 patients (19.4%) were included in the ABT group; 81 (52.3%) patients, comprising the standard management (STD) group, received neither ANH nor ABT. The ABT group had the worst prognosis among them. Before PSM, ANH was significantly associated with decreased RFS (P=0.043) and DSS (P=0.029) compared with the STD group before applying Bonferroni correction; however, no significant difference was observed after applying Bonferroni correction. Cox regression analysis identified ANH as an independent prognostic factor for RFS [relative risk (RR), 1.696; P=0.019] and DSS (RR, 1.876; P=0.009). After PSM, the ANH group exhibited less favorable RFS [median survival time (MST), 12.1 vs. 18.1 months; P=0.097] and DSS (MST, 32.1 vs. 50.5 months; P=0.097) compared with the STD group; however, these differences were not statistically significant. In conclusion, while ANH was not as harmful as ABT, it exhibited potentially more negative effects on long-term postoperative outcomes in PDAC than STD.

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Abbreviations: ABT, allogeneic blood transfusion; ANH, acute normovolemic hemodilution; DP, distal pancreatectomy; DSS, disease-specific survival; MST, median survival time; RFS, recurrence-free survival; RR, relative risk; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PSM, propensity score matching; STD, standard management; UICC, Union for International Cancer Control

Key words: ANH, blood transfusion, pancreatic neoplasms, prognosis, propensity score

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest solid cancers, worldwide (1,2). Surgery has long been considered a fundamental treatment option for this lethal disease (3-5). Despite ongoing improvements (6-11), pancreatic cancer surgery is often associated with significant intraoperative blood loss and the subsequent need for allogeneic blood transfusion (ABT) (12-14). The transfusion rate in patients who have undergone a pancreatic resection still falls in the 20 to 30% range, even when the procedure was performed by experienced surgeons in high-volume centers (13,15,16). Although ABT can be a lifesaving treatment during cancer surgery, it has been linked to a variety of negative outcomes from transfusion-related immunomodulation (TRIM) (14,17). Indeed, our previous study using propensity score matching analysis demonstrated the negative effects of intraoperative ABT on postoperative survival outcomes in patients with resectable PDAC (18). In order to minimize the use of ABT, the focus has been shifting to blood conservation strategies (19-21).

Acute normovolemic hemodilution (ANH) is an intraoperative blood conservation technique. ANH is performed immediately before the procedure and involves the removal of whole blood, while maintaining euvolemia with crystalloid and/or colloid solutions. ANH has been successfully performed in open-heart surgery since the 1970s (22,23). Subsequently, several studies, including those describing ANH use in various types of abdominal surgery, have shown that it is safe, inexpensive, and effectively reduces the need for

ABT (24-27). ANH also offers a medical solution that respects religious and cultural beliefs about the use of ABT. These results seem to indicate that ANH can compensate for the disadvantages of ABT and improve the prognosis of patients who undergo pancreatic resection for PDAC.

However, in contrast to evaluations of short-term performance, few reports have examined the association between ANH and long-term outcomes in cancer patients (21,28). Furthermore, there is no recorded evidence linking use of ANH with PDAC patients. Therefore, this study aimed to assess the impact of ANH on long-term outcomes in PDAC patients undergoing radical surgery. We herein present the potentially negative impact of ANH on long-term oncological outcomes in patients with PDAC.

Materials and methods

Patients and study design. This single-center, retrospective cohort study was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine (Aomori, Japan; reference no. 2022-032). Informed consent was obtained in the form of an opt-out system on our website (https://www.med.hirosaki-u.ac.jp/hospital/outline/resarch/resarch.html), which also had the approval of the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine. Our study did not include minors. This study was designed and carried out in accordance with the Declaration of Helsinki. The study workflow is shown in Fig. 1. A total of 155 patients undergoing curative pancreatic surgery for resectable PDAC at our facility between January 2007 and May 2018 were included in the study. A portion of the subjects in this study had been included in our previous study (18,29). Resectability status was made based on National Comprehensive Cancer Network guidelines. All patients had a confirmed pathologic diagnosis based on the 8th edition of the Union for International Cancer Control staging system for PDAC (30). In this study, we excluded the following cases: patients who had received neoadjuvant chemotherapy or anyone with remnant pancreatic cancer. Baseline clinicopathologic data were obtained from the medical records.

Patients were categorized according to whether or not they had received intraoperative ABT. Furthermore, patients who did not received intraoperative ABT were categorized according to whether or not they received ANH, and then compared. In this study, the patients who received both ANH and ABT were included in the ABT group. The patients who received neither ANH nor ABT were included in the standard management (STD) group. The primary analysis of this study was a comparison of the STD and the ANH group; a comparison of the ANH and the ABT group was performed as a sub-analysis. A comparison of the STD and the ABT group was not undertaken in this study because it had already been shown in previous studies (14,18).

Surgical procedures. We selected the type of pancreatic resection based on tumor location. Open pancreatoduodenectomy (PD) with lymph node dissection was usually conducted on cases of pancreatic head cancer during this study period. Reconstruction was typically done using a modified Child's method with an end-to-side pancreaticojejunostomy and an end-to-side choledochojejunostomy. All pancreaticojejunostomy anastomoses were conducted using a duct-to-mucosa technique. In cases of pancreatic body and tail cancer, an open or minimally invasive distal pancreatectomy (DP) was performed with lymph node dissection. If we detected swelling paraaortic lymph nodes, we generally performed paraaortic lymph node sampling during PD procedures whereas sampling was not routinely done during DP surgeries. After a PD, paraaortic lymph nodes were confirmed using standard histopathological assessment of corresponding paraffin-embedded, hematoxylin and eosin-stained material for surgical staging. Consequently, confirming whether or not the paraaortic lymph nodes were positive always occurred postoperatively. Regardless of whether there was paraaortic swelling or the paraaortic lymph nodes ended up testing positive, a pancreatectomy was performed in all cases. We performed a fresh frozen section analysis to confirm whether or not the pancreatic cut-end margin was clear of residual cancer. If residual cancer was present at the pancreatic cut end margin, we cut the pancreas further to reach negative margin status. If necessary, to achieve a curative resection, we performed a total pancreatectomy with lymph node dissection.

During this study, all surgical procedures were carried out by board certified surgeons. We classified surgeons into two groups in the same manner as a previous publication (31): junior surgeons, those whose surgical training experience was 10 years or less, and senior surgeons, those who had over 10 years of surgical training. All junior surgeons conducted surgeries with attending surgeons.

ANH protocol. Details of the ANH protocol are described in detail in other papers (32). Briefly, the principal indication for ANH at our institution is an estimated blood loss of more than 500 ml or a request from a surgeon for a patient with a hemoglobin (Hb) level of more than 10 g/dl. Patients with uncontrolled congenital heart failure including active ischemic heart disease, severe liver disease, or renal failure were excluded. After anesthetic induction, blood was withdrawn through the central venous line, and the withdrawn blood volume for ANH was selected to avoid a Hb level of less than 8 g/dl after hemodilution. The withdrawn blood volume was simultaneously replaced with an equal volume of 6% hydroxyethyl starch solution (130/4) (Volven; Fresenius Kabi, Bad Homburg, Germany). The blood collected was stored in a standard blood collection pack (JMS Blood Bag CPD400; JMS, Tokyo, Japan) at room temperature on a shaker in the operating room. The collected blood was then reinfused into the patients after specimen procurement.

Transfusion protocol. In the current study, intraoperative ABT was defined as the transfusion of red blood cell concentrate during the operation. At our institution, the intraoperative transfusion trigger was set at Hb <7 g/dl. Additionally, for cases involving an increased risk of ischemia, such as patients with preexisting concomitant pulmonary disease, coronary artery disease, or cerebral vascular disease, and those showing signs of cardiac ischemia based on new electrocardiographic information, the transfusion threshold was set at a Hb level of less than 9 g/dl. For the ANH group, if the trigger point was reached, autologous blood was given first. Allogeneic blood

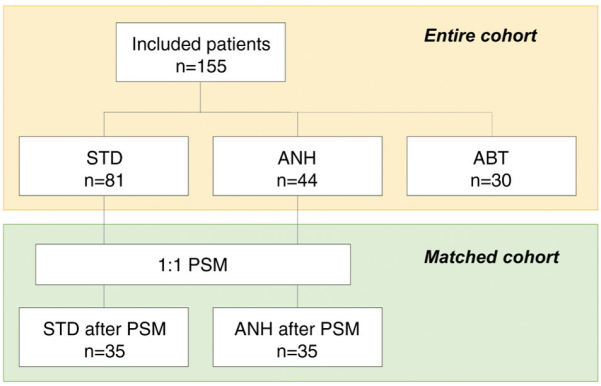

Figure 1. Study workflow. ABT, allogeneic blood transfusion; ANH, acute normovolemic hemodilution; PSM, propensity score matching; STD, standard management.

was used only after all autologous blood had been reinfused and the Hb remained at less than 7 g/dl.

Definition of intraoperative blood loss. Intraoperative blood loss was calculated based on the in/out balance of the operative field. At our institution, any fluid loss from the abdominal cavity including ascites, bile, and lymphatics is considered to be intraoperative bleeding. In this study, we estimated the circulating blood volume (CBV) using the following formula: CBV (ml)=70 x body weight (kg).

Definition of postoperative complications. In this study, postoperative complications were graded using the Clavien-Dindo classification system (33). Pancreatic fistula was defined and graded based on criteria outlined by the International Study Group of Pancreatic Fistula (ISGPF) (34), while Delayed Gastric Emptying was defined and graded according to criteria outlined by the International Study Group of Pancreatic Surgery (ISGPS) (35).

Statistical analysis. Continuous variables were expressed as medians (ranges) and analyzed using nonparametric methods for non-normally distributed data (Mann-Whitney U-test). Categorical variables were reported as numbers (percentages) and analyzed using the chi-squared test or Fisher's exact test, as appropriate. Additionally, in order to compare each group pairwise, Bonferroni correction was applied to the Mann-Whitney U-test/chi-squared test/Fisher's exact test (P-values were multiplied by three). Patients in the STD and the ANH groups were classified using the propensity score matching (PSM) method to minimize the impact of possible selective bias in the survival analysis. Propensity scores were based on the selected covariates, which were significantly associated with ANH in univariate analysis (P<0.1), including sex, age, body weight, C-reactive protein (CRP), and total bilirubin. In addition, based on the consensus reached at expert meetings during this study, the surgical procedure was also included in the covariate with which propensity scores were calculated. We did not include hemoglobin and hematocrit in the covariate. Nearest neighbor matching was performed in a one-to-one ratio without replacement. A caliper width of 0.08 was used to avoid bad matches. Recurrence-free survival (RFS) and Disease-specific survival (DSS) were calculated using the Kaplan-Meier method, and differences in the survival rates were compared using the log-rank test. We used Bonferroni correction for survival analysis. RFS was defined as the time from the operation to the date of disease recurrence. DSS was defined as the time from the operation to the time of death due to PDAC, or the last follow-up time. This study was planned with a maximum follow-up period of five years. Both univariate and multivariate analyses were conducted using Cox proportional hazards regression to identify independent predictors of RFS and DSS, with only significant variables from the univariate analysis included in the multivariate analysis. In this analysis, we divided continuous variables into two groups according to median values. A difference was considered to be significant for values of P<0.05. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, NY, USA).

Results

Comparison of the ABT rate between patients with/without ANH. We collected a dataset from 155 resectable cases of PDAC. First, we evaluated how much ANH reduced the need for ABT. Among the 109 patients who did not receive ANH, eight (7.3%) exhibited low hemoglobin levels (less than 10 g/dl) before surgery, and 28 (25.7%) required ABT. On the other hand, of the 46 patients who received ANH, only two patients (4.3%) needed ABT. The ABT rate in the ANH implementation group was significantly lower than in the non-implementation group (P=0.002). Of the total of 155 patients, 44 (28.4%) fell into the ANH group and 30 (19.4%) made up the ABT group. Eighty-one (52.3%) patients received neither ANH nor ABT.

Comparison of the clinicopathological characteristics across the groups. Next, we investigated the clinical characteristics across the groups (Table I). The ANH group was significantly associated with higher preoperative Hb and hematocrit levels compared to the other groups. The ANH group had a higher mean age and showed higher CRP levels than the STD group. Tumor biomarkers and pathological findings revealed minor differences between the STD and the ANH groups. These data indicated that the preoperative condition of the patients in the ANH group was no worse than that of the STD group.

Comparison of the operative and postoperative outcomes across the groups. There was a trend toward a higher proportion of distal pancreatectomy in the STD group than in the ANH group (45.7% vs. 29.5%, P=0.157) (Table II). In comparison with the STD group, one of the key features of the ANH group was longer operation time (250 vs. 346 min, P<0.001) and anesthesia time (317 vs. 405 min, P<0.001), with more intraoperative blood loss (420 vs. 983 ml, P<0.001) and a higher volume of intraoperative fluids administered (2,850 vs. 4,975 ml, P<0.001). When we evaluated the intraoperative in-out balance by correcting for body weight and anesthesia time, we found no difference between the two groups.

Regarding the postoperative short-term outcomes, the ANH group displayed a higher frequency of postoperative complications (Clavien-Dindo grade ≥3, 3.4-fold, P=0.012) compared to the STD group. Specifically, there were more clinically

Table I. Comparison of clinicopathological characteristics for the entire cohort.

Characteristics	All (n=155)	STD (n=81)	ANH (n=44)	ABT (n=30)	P-value (STD vs. ANH)	P-value (ANH vs. ABT)
Sex, male	79 (51.0)	34 (42.0)	29 (65.9)	16 (53.3)	0.021	0.553
Age, years	70 (49-85)	71 (50-85)	67 (49-78)	71 (50-80)	0.026	0.835
Body mass index, kg/m^2	22.3 (14.1-36.3)	22.0 (15.8-29.5)	22.8 (14.1-33.3)	24.2 (16.4-36.3)	0.715	0.362
ASA-PS					0.354[b]	0.415[b]
PS2	126 (81.3)	64 (79.0)	39 (88.6)	23 (76.7)		
PS3	29 (18.7)	17 (21.0)	5 (11.4)	7 (23.3)		
Preoperative biliary drainage	53 (34.2)	22 (27.2)	18 (40.9)	13 (43.3)	0.231	>0.999
Laboratory values						
Hemoglobin, g/dl	12.7 (7.2-16.5)	12.7 (7.2-15.9)	13.8 (10.8-16.3)	11.6 (8.8-16.5)	0.007	<0.001
CRP, mg/dl	0.12 (0.02-9.59)	0.10 (0.02-9.59)	0.31 (0.02-6.50)	0.23 (0.02-4.91)	0.010	0.857
Albumin, g/dl	3.9 (2.0-5.7)	3.9 (2.5-5.7)	4.1 (2.4-4.9)	3.8 (2.0-4.5)	0.573	0.024
Hemoglobin A1c, %	6.1 (4.4-12.8)	6.1 (4.4-12.8)	6.4 (4.4-11.9)	5.9 (4.7-8.7)	>0.999	0.292
Creatinine, mg/dl	0.67 (0.40-2.02)	0.66 (0.43-2.02)	0.70 (0.41-1.30)	0.67 (0.40-1.43)	0.636	>0.999
AST, U/l	29 (11-406)	27 (13-406)	27 (11-241)	52 (12-260)	>0.999	0.051
ALT, U/l	35 (9-627)	25 (9-621)	33 (12-616)	68 (9-627)	0.420	0.158
Total bilirubin, mg/dl	0.7 (0.2-32.7)	0.6 (0.2-32.7)	0.8 (0.2-24.0)	2.6 (0.3-24.1)	0.066	0.391
CA19-9, U/ml	92 (1-9,675)	57 (1-3,199)	118 (5-9,675)	135 (1-6,370)	0.345	0.969
CEA, ng/ml	2.7 (0.5-37.0)	2.8 (0.6-37.0)	2.5 (0.5-23.9)	3.6 (0.5-10.5)	0.776	0.238
Operative variables						
Procedure					0.178[b]	0.044[b]
Pancreaticoduodenectomy	95 (61.3)	39 (48.1)	30 (68.2)	26 (86.7)		
Distal pancreatectomy	52 (33.5)	37 (45.7)	13 (29.5)	2 (6.7)		
Total pancreatectomy	8 (5.2)	5 (6.2)	1 (2.3)	2 (6.7)		
Portal vein resection	25 (16.1)	8 (9.9)	8 (18.2)	9 (30.0)	0.369	0.471
Grouping of surgeons					>0.999[b]	0.890[b]
Junior surgeon	10 (6.5)	6 (7.4)	1 (2.3)	3 (10.0)		
Senior surgeon	145 (93.5)	75 (92.6)	43 (97.7)	27 (90.0)		
Pathology						
Tumor size, mm	30 (7-150)	29 (7-150)	33 (10-130)	35 (15-57)	0.753	>0.999
UICC 8th edition						
T category					0.726[b]	0.620[b]
T1	20 (12.9)	10 (12.3)	8 (18.2)	2 (6.7)		
T2	92 (59.4)	51 (63.0)	22 (50.0)	19 (63.3)		
T3	43 (27.7)	20 (24.7)	14 (31.8)	9 (30.0)		
T4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
N category					0.473	0.749
N0	62 (40.0)	38 (46.9)	17 (38.6)	7 (23.3)		
N1	58 (37.4)	31 (38.3)	15 (34.1)	12 (40.0)		
N2	35 (22.6)	12 (14.8)	12 (27.3)	11 (36.7)		
M category					0.065[b]	0.263[b]
M0	144 (92.9)	78 (96.3)	37 (84.1)	29 (96.7)		
M1[a]	11 (7.1)	3 (3.7)	7 (15.9)	1 (3.3)		
UICC stage					0.018[b]	0.179[b]
IA	12 (7.7)	6 (7.4)	5 (11.4)	1 (3.3)		
IB	24 (15.5)	17 (21.0)	3 (6.8)	4 (13.3)		
IIA	12 (7.7)	4 (4.9)	7 (15.9)	1 (3.3)		
IIB	72 (46.5)	41 (50.6)	15 (34.1)	16 (53.3)		
III	24 (15.5)	10 (12.3)	7 (15.9)	7 (23.3)		
IV	11 (87.1)	3 (3.7)	7 (15.9)	1 (3.3)		

Table I. Continued.

Characteristics	All (n=155)	STD (n=81)	ANH (n=44)	ABT (n=30)	P-value (STD vs. ANH)	P-value (ANH vs. ABT)
R0 resection	141 (91.0)	75 (92.6)	38 (86.4)	28 (93.3)	0.683	0.921

[a]All of the patients were diagnosed with M1 due to positive lymph nodes other than the regional lymph nodes. Continuous variables are presented as the median (range) and were analyzed using the Mann-Whitney U-test. Categorical variables are reported as the number (percentage) and were analyzed using the χ^2 test or Fisher's exact test, as appropriate. [b]Fisher's exact test was performed, while other comparisons for categorical variables were carried out using the χ^2 test. All P-values presented were corrected using Bonferroni adjustments. ABT, allogeneic blood transfusion; ALT, alanine aminotransferase; ANH, acute normovolemic hemodilution; ASA-PS, American Society of Anesthesiologists physical status; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; STD, standard management; UICC, Union for International Cancer Control.

relevant postoperative pancreatic fistulas in the ANH group (2.4-fold, P=0.118). Moreover, the ANH groups experienced longer postoperative hospital stays (P=0.007). There was no in-hospital or 90-day mortality for any patients in this study. In short, postoperative short-term outcomes in the ANH group were less favorable than those in the STD group, but not as poor as that of the ABT group.

Comparison of the survival outcomes of the entire cohort. The groups were well matched in the proportion of adjuvant chemotherapy (Table II). The median follow-up period was 30.7 months (range: 4.2-60.0). A total of 117 patients (75.5%) had recurrences. The median RFS time was 13.0 months for the entire cohort. A total of 101 patients (65.2%) died due to the primary disease during the follow-up period. The median DSS time was 32.1 months for the entire cohort. The RFS and DSS curves for patients classified as requiring intraoperative blood management are shown in Fig. 2A and B. The RFS time was significantly shorter in the ANH group than in the STD group (median survival time (MST), 11.1 vs. 16.5 months, P=0.043 before correction). Likewise, the DSS was significantly shorter in the ANH group (MST, 28.6 vs. 41.6 months, P=0.029 before correction). However, these differences were not significant after Bonferroni correction (RFS, P=0.129; DSS, P=0.087). In the comparison between ANH and ABT, RFS was not significantly different between the two groups (MST, 11.1 vs. 9.5 months, P=0.143, before applying Bonferroni correction; P=0.429, after correction). The ANH group showed a longer DSS time than the ABT group, but it was not significant (MST, 28.6 vs. 19.7 months, P=0.136, before applying Bonferroni correction; P=0.408, after correction). Taken together, these data suggest that ANH has a negative impact on the postoperative long-term outcomes in PDAC, though not as severe as ABT.

Clinicopathological characteristics influencing RFS and DSS of the STD and ANH groups. To assess whether ANH influences RFS and DSS in PDAC, we further performed Cox regression analysis. Since red blood cell transfusion has been shown to affect cancer prognosis negatively (18), we evaluated the clinicopathological factors influencing RFS and DSS in subjects, excluding the ABT group. In univariate analysis, significant predictors of decreased RFS were preoperative CRP, preoperative aspartate aminotransferase, preoperative carbohydrate antigen 19-9 (CA19-9), tumor size, Union for International Cancer Control (UICC) T category, UICC N category, ANH, and adjuvant chemotherapy. In multivariate analysis, preoperative CA19-9≥68 U/ml (relative risk (RR)=1.796 (95% confidence interval (CI), 1.124-2.871), P=0.014), UICC N1-2 (RR=2.207 (95% CI, 1.339-3.638), P=0.002), ANH (RR=1.696 (95% CI, 1.091-2.636), P=0.019), and adjuvant chemotherapy (RR=0.345 (95% CI, 0.204-0.584), were independent prognostic factors for RFS (Table III).

Likewise, in univariate analysis, significant predictors of decreased DSS were preoperative CRP, preoperative aspartate aminotransferase, UICC T category, UICC N category, ANH, and adjuvant chemotherapy. In multivariate analysis, UICC T2-3 (RR=3.045 (95% CI, 1.071-8.657), P=0.037), UICC N1-2 (RR=2.225 (95% CI, 1.275-3.883), P=0.005), ANH (RR=1.876 (95% CI, 1.174-2.998), P=0.009), and adjuvant chemotherapy (RR=0.268 (95% CI, 0.151-0.477), P<0.001) were independent prognostic factors for DSS (Table IV). These results provide us with a warning that ANH falls in the poor prognostic factor category with regard to the management of resectable PDAC.

Propensity score matching analysis. To reduce confounding biases and confirm the influence of ANH, we further performed PSM analysis between the STD and the ANH groups. After one-to-one PSM, 35 pairs of patients were included in further analysis. The comparison of the clinicopathological characteristics between the STD group and the ANH group, after matching, is shown in Table V. After PSM, the ANH group showed a longer operation time (327 vs. 261 min, P=0.042), with more intraoperative blood loss (970 vs. 570 ml, P<0.001) compared to the STD group. The ANH group was also administered a higher volume of intraoperative fluids (4,850 vs. 3,200 ml, P<0.001) and showed more intraoperative in-out balance than the STD group. However, after correcting the balance by body weight and anesthesia time, there was no difference between the two groups (Table VI).

Next, we evaluated the postoperative complications in the matched cohort. As a result, there were no significant differences in the incidences of postoperative complications between the two groups after PSM (Table VI). Furthermore, we performed a survival analysis of the matched cohort. RFS time was slightly but not significantly poorer in the ANH group

Table II. Comparison of operative and postoperative outcomes for the entire cohort.

Outcomes	All (n=155)	STD (n=81)	ANH (n=44)	ABT (n=30)	P-value (STD vs. ANH)	P-value (ANH vs. ABT)
Operative results						
Operation time, min	307 (91-647)	250 (91-619)	346 (129-587)	368 (127-647)	<0.001	0.206
Anesthesia time, min	372 (172-757)	317 (172-676)	405 (187-680)	429 (209-757)	<0.001	0.327
Intraoperative blood loss, ml	750 (50-5,600)	420 (50-2,400)	983 (150-2,775)	1,940 (540-5,600)	<0.001	<0.001
Intraoperative blood loss, ml/kg	14.1 (0.8-77.6)	7.9 (0.8-42.6)	18.3 (2.3-39.0)	29.5 (13.9-77.6)	<0.001	<0.001
IBL >20% in CBV	78 (50.3)	20 (24.7)	29 (65.9)	29 (96.7)	<0.001	0.003
Blood volume removed, ml	0 (0-800)	0 (0-0)	800 (400-800)	0 (0-800)	<0.001	<0.001
Intraoperative fluid given, ml	3,600 (200-9,000)	2,850 (1,300-7,500)	4,150 (2,500-7,300)	4,688 (200-9,000)	<0.001	>0.999
Intraoperative albumin, ml	0 (0-1,250)	0 (0-500)	0 (0-1,000)	500 (0-1,250)	0.001	<0.001
Intraoperative RBC, ml	0 (0-1,400)	0 (0-0)	0 (0-0)	560 (80-1,400)	-	<0.001
Intraoperative FFP, ml	0 (0-960)	0 (0-480)	0 (0-0)	0 (0-960)	>0.999	<0.001
Intraoperative PC, ml	0 (0-200)	0 (0-0)	0 (0-0)	0 (0-200)	-	0.169
Total fluid volume administered, ml	3,900 (1,300-11,510)	2,850 (1,300-8,000)	4,975 (2,950-8,850)	5,885 (2,530-11,510)	<0.001	0.411
Intraoperative urine output, ml	480 (20-3,800)	420 (56-1,550)	545 (20-1,750)	598 (70-3,800)	0.080	>0.999
Total in-out balance, ml	2,300 (410-7,714)	1,880 (485-5,500)	2,735 (1,190-4,700)	3,072 (410-7,714)	<0.001	>0.999
Total in-out balance, ml/kg/h[a]	6.7 (1.2-13.9)	6.4 (1.8-12.4)	6.7 (3.2-13.9)	7.2 (1.2-13.7)	0.627	>0.999
Postoperative results						
Postoperative complications (Clavien-Dindo classification grade ≥3)	27 (17.4)	6 (7.4)	11 (25.0)	10 (33.3)	0.012	0.870
Pancreatic fistula (ISGPF grade ≥B)	24 (15.5)	7 (8.6)	9 (20.4)	8 (26.7)	0.118	>0.999
Delayed gastric emptying (ISGPS grade ≥B)	17 (11.0)	7 (8.6)	6 (13.6)	4 (13.3)	0.756	>0.999[b]
Postoperative hospital stay, days	19 (6-73)	17 (7-73)	22 (6-64)	31 (10-57)	0.007	0.585
90-day mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Adjuvant chemotherapy	122 (80.3)	64 (80.0)	34 (79.1)	24 (82.8)	>0.999	>0.999

[a]Estimated using the following formula: Total in-out balance/body weight (kg)/anesthesia time (h). Continuous variables are presented as the median (range) and were analyzed using the Mann-Whitney U-test. Categorical variables are reported as the number (percentage) and were analyzed using the χ^2 test or Fisher's exact test, as appropriate. [b]Fisher's exact test was performed, while other comparisons for categorical variables were carried out using the χ^2 test. All P-values presented were corrected using Bonferroni adjustments. ABT, allogeneic blood transfusion; ANH, acute normovolemic hemodilution; CBV, circulating blood volume; FFP, fresh frozen plasma; IBL, intraoperative blood loss; ISGPF, International Study Group of Pancreatic Fistula; ISGPS, International Study Group of Pancreatic Surgery; PC, platelet concentration; RBC, red blood cells; STD, standard management.

compared with the STD group (MST, 12.1 vs. 18.1 months, P=0.097; Fig. 2C). In addition, a similar trend was noted in the DSS rate (MST, 32.1 vs. 50.5 months, P=0.097; Fig. 2D). After PSM, in contrast with short-term outcomes, postoperative long-term outcomes in the ANH group were less favorable than those in the STD group.

To assess whether ANH influences RFS and DSS in the matched cohort, we performed a Cox regression analysis. As

Table III. Clinicopathological characteristics predicting RFS in the standard management and ANH groups.

				Univariate analysis			Multivariate analysis		
Characteristics	No.	5-year RFS, %	MST, months	RR	95% CI	P-value	RR	95% CI	P-value
Sex				0.766	0.505-1.162	0.235			
Male	63	24.9	12.4						
Female	62	27.6	16.5						
Age, years				1.210	0.800-1.831	0.365			
<70	65	28.1	17.9						
≥70	60	23.7	13.0						
Body mass index, kg/m^2				1.019	0.674-1.541	0.871			
<22.1	62	28.3	14.2						
≥22.1	63	24.2	15.2						
Preoperative biliary drainage				1.148	0.737-1.788	0.540			
No	85	26.7	15.8						
Yes	40	25.6	12.4						
Hemoglobin, g/dl				1.088	0.719-1.647	0.689			
<12.9	65	25.0	15.8						
≥12.9	60	28.8	12.4						
CRP, mg/dl				1.613	1.050-2.478	0.022	0.982	0.619-1.556	0.937
<0.11	60	35.5	21.6						
≥0.11	65	17.4	12.7						
Albumin, g/dl				1.013	0.670-1.534	0.933			
<3.9	64	22.2	15.7						
≥3.9	61	30.2	14.2						
Hemoglobin A1c, %				1.240	0.799-1.924	0.477			
<6.0	58	25.2	13.0						
≥6.0	55	10.3	12.7						
Creatinine, mg/dl				0.822	0.542-1.247	0.356			
<0.67	66	21.6	13.4						
≥0.67	59	31.6	17.5						
AST, U/l				1.775	1.168-2.700	0.006	1.108	0.669-1.834	0.691
<27	64	36.3	21.2						
≥27	61	15.4	12.1						
ALT, U/l				1.420	0.937-2.152	0.096			
<28	63	32.4	17.7						
≥28	62	19.6	12.4						
Total bilirubin, mg/dl				1.135	0.749-1.720	0.551			
<0.7	67	24.8	17.5						
≥0.7	58	27.1	12.3						
CA19-9, U/ml				1.897	1.250-2.880	0.002	1.796	1.124-2.871	0.014
<68	63	35.1	21.6						
≥68	62	17.4	11.2						
CEA, ng/ml				1.316	0.870-1.990	0.192			
<2.7	67	30.2	16.5						
≥2.7	58	21.7	13.4						
Tumor size, mm				1.807	1.193-2.737	0.005	1.229	0.777-1.944	0.379
<30	71	33.5	17.9						
≥30	54	16.2	9.8						
UICC T category				3.300	1.522-7.154	0.001	2.026	0.864-4.750	0.104
T1	18	58.3	42.8						
T2-3	107	20.7	12.4						

Table III. Continued.

Characteristics	No.	5-year RFS, %	MST, months	Univariate analysis			Multivariate analysis		
				RR	95% CI	P-value	RR	95% CI	P-value
UICC N category				2.552	1.635-3.983	<0.001	2.207	1.339-3.638	0.002
N0	55	43.9	39.8						
N1-2	70	12.1	12.3						
UICC M category				1.804	0.903-3.607	0.090			
M0	115	27.5	15.2						
M1[a]	10	10.0	8.3						
R0 resection				0.787	0.380-1.628	0.831			
No	12	33.3	13.0						
Yes	113	25.4	14.5						
Procedure				0.878	0.573-1.345	0.550			
PD, TP	75	22.4	13.6						
DP	50	31.7	15.7						
Portal vein resection				1.235	0.686-2.225	0.480			
No	109	28.2	14.5						
Yes	16	0.0	13.6						
Operation time, min				1.420	0.938-2.150	0.096			
<275	63	33.3	17.5						
≥275	62	17.4	12.4						
Anesthesia time, min				1.182	0.782-1.789	0.427			
<363	63	30.6	15.8						
≥363	62	20.6	12.4						
Intraoperative blood loss, ml				1.330	0.876-2.018	0.179			
<600	63	34.3	15.1						
≥600	62	17.9	14.2						
ANH				1.545	1.010-2.364	0.043	1.696	1.091-2.636	0.019
No	81	30.3	16.5						
Yes	44	18.3	11.1						
Intraoperative fluid given, ml			0.951	0.627-1.441	0.812				
<3,500	68	26.9	14.2						
≥3,500	57	24.3	17.9						
Intraoperative urine output, ml				1.262	0.834-1.910	0.269			
<465	64	29.6	16.5						
≥465	61	22.2	12.7						
Total in-out balance, ml				1.067	0.705-1.615	0.759			
<2,210	63	27.0	15.7						
≥2,210	62	24.6	13.4						
Total in-out balance, ml/kg/h				1.354	0.894-2.048	0.213			
<6.6	62	28.5	17.5						
≥6.6	63	23.7	11.3						
Postoperative complications				1.302	0.723-2.346	0.377			
Clavien-Dindo grade 0-2	108	26.5	15.7						
Clavien-Dindo grade ≥3	17	23.5	12.1						
Pancreatic fistula				1.270	0.691-2.333	0.440			
ISGPF grade non-A	109	26.2	15.1						
ISGPF grade B-C	16	25.0	12.1						

Table III. Continued.

Characteristics	No.	5-year RFS, %	MST, months	Univariate analysis			Multivariate analysis		
				RR	95% CI	P-value	RR	95% CI	P-value
Postoperative hospital stay, days				1.104	0.730-1.669	0.640			
<17	64	26.6	15.7						
≥17	61	25.2	13.0						
Adjuvant chemotherapy				0.535	0.332-0.862	0.003	0.345	0.204-0.584	<0.001
No	27	8.0	9.3						
Yes	98	30.5	16.5						

[a]All of the patients were diagnosed with M1 due to positive lymph nodes other than the regional lymph nodes. Since red blood cell transfusion has been shown to affect cancer prognosis negatively (18), the clinicopathological factors influencing RFS in subjects, excluding the ABT group, were evaluated. P-values were obtained using Cox regression analysis. ALT, alanine aminotransferase; ANH, acute normovolemic hemodilution; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DP, distal pancreatectomy; ISGPF, International Study Group of Pancreatic Fistula; MST, median survival time; PD, pancreatoduodenectomy; RFS, recurrence-free survival; RR, relative risk; TP, total pancreatectomy; UICC, Union for International Cancer Control.

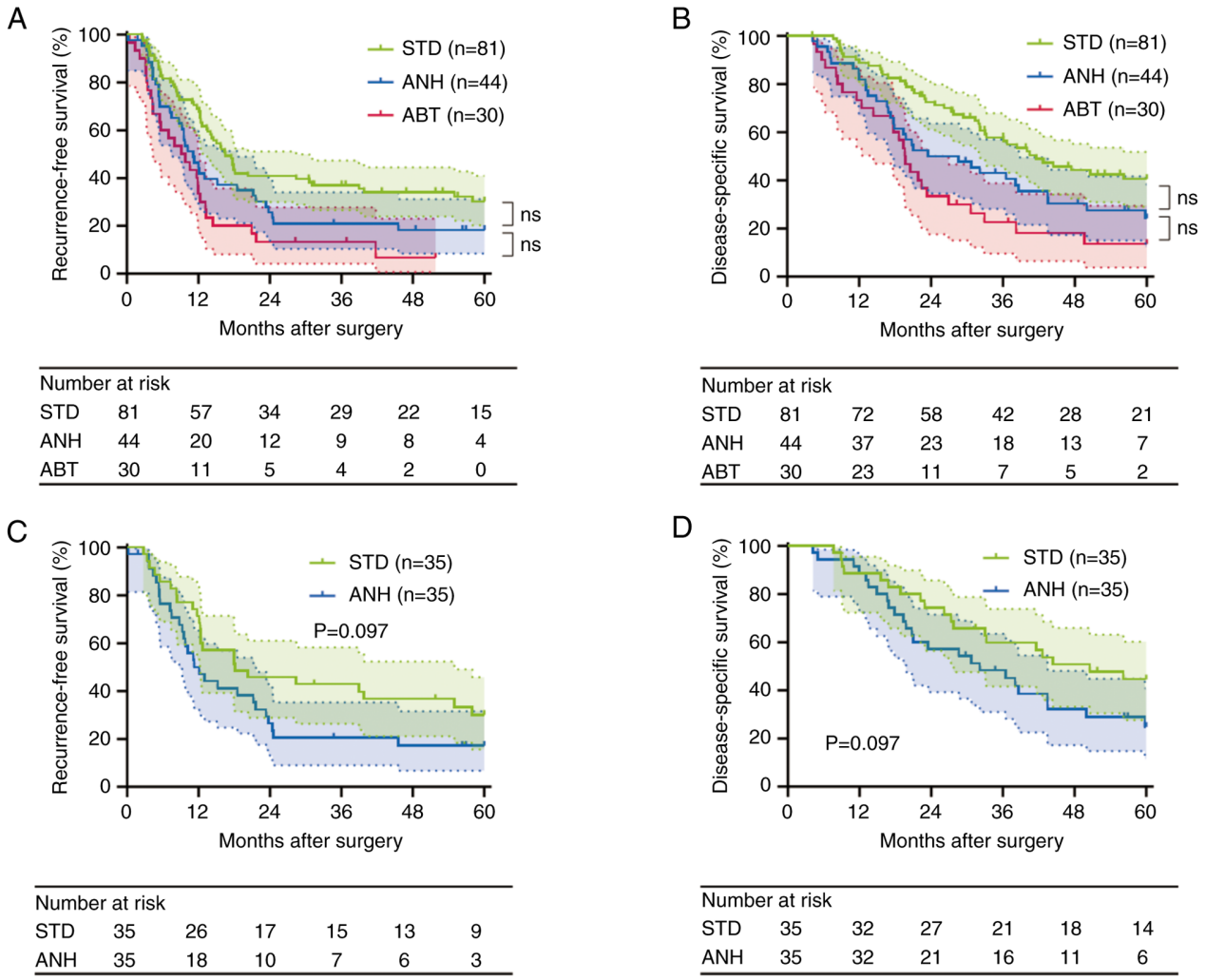

Figure 2. Survival analysis. (A and B) Survival cures of the STD, ANH and ABT groups for the entire cohort. (A) Recurrence-free survival (STD vs. ANH, P=0.043; ANH vs. ABT, P=0.143; log-rank test, before applying Bonferroni correction; after correction: STD vs. ANH, P=0.129; ANH vs. ABT, P=0.429). (B) Disease-specific survival (STD vs. ANH, P=0.029; ANH vs. ABT, P=0.136; log-rank test, before applying Bonferroni correction; after correction: STD vs. ANH, P=0.087; ANH vs. ABT, P=0.408). (C and D) Survival cures of the STD and ANH groups in the propensity score-matched cohort. (C) Recurrence-free survival (P=0.097; log-rank test). (D) Disease-specific survival (P=0.097; log-rank test). ABT, allogeneic blood transfusion; ANH, acute normovolemic hemodilution; ns, not significant; STD, standard management.

Table IV. Clinicopathological characteristics predicting DSS in the standard management and ANH groups.

				Univariate analysis			Multivariate analysis		
Characteristics	No.	5-year DSS, %	MST, months	RR	95% CI	P-value	RR	95% CI	P-value
Sex				0.645	0.408-1.020	0.070			
Male	63	28.8	32.1						
Female	62	41.6	40.0						
Age, years				1.427	0.908-2.242	0.121			
<70	65	42.0	42.6						
≥70	60	27.1	32.2						
Body mass index, kg/m^2				0.920	0.586-1.442	0.811			
<22.1	62	36.0	33.2						
≥22.1	63	33.9	42.6						
Preoperative biliary drainage				1.418	0.889-2.263	0.141			
No	85	39.1	38.6						
Yes	40	25.5	28.6						
Hemoglobin, g/dl				0.957	0.609-1.505	0.850			
<12.9	65	33.7	36.5						
≥12.9	60	35.9	38.6						
CRP, mg/dl				1.617	1.013-2.581	0.025	0.931	0.566-1.532	0.779
<0.11	60	44.8	50.0						
≥0.11	65	24.2	32.2						
Albumin, g/dl				1.063	0.677-1.668	0.913			
<3.9	64	32.7	38.6						
≥3.9	61	37.2	36.5						
Hemoglobin A1c, %				1.134	0.703-1.832	0.254			
<6.0	58	41.6	42.6						
≥6.0	55	28.7	33.2						
Creatinine, mg/dl				0.891	0.567-1.400	0.616			
<0.67	66	30.2	38.1						
≥0.67	59	40.0	36.5						
AST, U/l				1.609	1.023-2.531	0.038	1.422	0.831-2.434	0.119
<27	64	42.0	43.5						
≥27	61	26.9	29.4						
ALT, U/l				1.349	0.859-2.119	0.192			
<28	63	40.0	41.6						
≥28	62	29.5	32.2						
Total bilirubin, mg/dl				1.236	0.788-1.939	0.355			
<0.7	67	35.7	40.0						
≥0.7	58	33.1	32.2						
CA19-9, U/ml				1.524	0.970-2.395	0.066			
<68	63	40.4	42.6						
≥68	62	29.4	31.4						
CEA, ng/ml				1.418	0.904-2.224	0.126			
<2.7	67	40.2	40.0						
≥2.7	58	28.2	31.4						
Tumor size, mm				1.499	0.955-2.352	0.076			
<30	71	41.6	38.1						
≥30	54	26.0	36.5						

Table IV. Continued.

Characteristics	No.	5-year DSS, %	MST, months	Univariate analysis			Multivariate analysis		
				RR	95% CI	P-value	RR	95% CI	P-value
UICC T category				4.570	1.667-12.530	0.001	3.045	1.071-8.657	0.037
T1	18	73.8	53.0						
T2-3	107	28.4	32.1						
UICC N category				2.245	1.387-3.634	0.001	2.225	1.275-3.883	0.005
N0	55	52.1	42.8						
N1-2	70	20.8	28.6						
UICC M category				1.521	0.758-3.051	0.235			
M0	115	37.8	38.1						
M1[a]	10	0	30.8						
R0 resection				1.239	0.595-2.578	0.278			
No	12	31.3	21.0						
Yes	113	35.3	38.3						
Procedure				0.829	0.520-1.322	0.430			
PD, TP	75	31.6	36.1						
DP	50	39.6	38.6						
Portal vein resection				1.015	0.487-2.112	0.969			
No	109	34.0	38.1						
Yes	16	44.4	33.0						
Operation time, min				1.357	0.864-2.129	0.183			
<275	63	39.5	40.4						
≥275	62	29.6	33.0						
Anesthesia time, min				1.131	0.721-1.774	0.591			
<363	63	37.5	38.3						
≥363	62	31.8	36.5						
Intraoperative blood loss, ml				1.180	0.752-1.851	0.471			
<600	63	37.8	38.6						
≥600	62	31.8	36.5						
ANH				1.651	1.046-2.605	0.029	1.876	1.174-2.998	0.009
No	81	40.6	41.6						
Yes	44	24.1	23.5						
Intraoperative fluid given, ml				1.017	0.647-1.600	0.941			
<3,500	68	33.1	36.7						
≥3,500	57	36.7	36.5						
Intraoperative urine output, ml				1.461	0.930-2.295	0.098			
<465	64	40.8	42.6						
≥465	61	27.9	33.2						
Total in-out balance, ml				1.174	0.748-1.842	0.484			
<2,210	63	35.0	40.0						
≥2,210	62	34.8	36.1						
Total in-out balance, ml/kg/h				1.405	0.895-2.204	0.260			
<6.6	62	37.2	40.4						
≥6.6	63	32.6	33.0						
Postoperative complications				1.440	0.792-2.620	0.229			
Clavien-Dindo grade 0-2	108	37.7	36.7						
Clavien-Dindo grade ≥3	17	19.9	43.5						

Table IV. Continued.

Characteristics	No.	5-year DSS, %	MST, months	Univariate analysis			Multivariate analysis		
				RR	95% CI	P-value	RR	95% CI	P-value
Pancreatic fistula				1.421	0.767-2.635	0.262			
ISGPF grade non-A	109	37.2	36.7						
ISGPF grade B-C	16	21.4	21.2						
Postoperative hospital stay, days				1.201	0.765-1.885	0.425			
<17	64	39.8	38.1						
≥17	61	29.9	36.5						
Adjuvant chemotherapy				0.407	0.247-0.671	<0.001	0.268	0.151-0.477	<0.001
No	27	9.1	20.8						
Yes	98	41.2	42.6						

[a]All of the patients were diagnosed with M1 due to positive lymph nodes other than the regional lymph nodes. Since red blood cell transfusion has been shown to affect cancer prognosis negatively (18), the clinicopathological factors influencing DSS in subjects, excluding the ABT group, were evaluated. P-values were obtained using Cox regression analysis. ALT, alanine aminotransferase; ANH, acute normovolemic hemodilution; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DP, distal pancreatectomy; DSS, disease-specific survival; ISGPF, International Study Group of Pancreatic Fistula; MST, median survival time; PD, pancreatoduodenectomy; RR, relative risk; TP, total pancreatectomy; UICC, Union for International Cancer Control.

a result, we identified some factors that had a greater effect on poor prognosis than ANH (Table SI).

Discussion

This report represents the first study to examine the effect of ANH on PDAC prognosis longitudinally. This study demonstrated that ANH has a negative impact on long-term outcomes in PDAC compared to standard management, though not as negative as ABT. Similar results were confirmed even after propensity score matching analysis. These results elucidate the potential negative effects of ANH compared to management without transfusion in resectable PDAC.

Despite the proven short-term outcomes (36,37), there are surprisingly few studies evaluating the long-term effects of ANH on cancer patients. A recent post-hoc analysis from a prospective trial demonstrated that ANH did not have any detrimental effects on long-term oncologic outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer (21). In the field of gastroenterology, an RCT evaluating ANH during major hepatectomy procedures for metastatic colorectal cancer showed no detrimental impact of ANH on survival outcomes (28). These findings are the opposite of our results. However, the studies were originally conducted to determine if ANH reduced the need for ABT. In short, these post-hoc analyses comparing the long-term outcomes between the STD and ANH groups included patients who received ABT. This heterogeneity may have affected the survival outcomes, because ABT can cause an immunomodulatory effect leading to worse oncologic outcomes (17). Thus, we excluded patients who received ABT and then directly compared the ANH and STD groups. As a result, our study figured out the potential differences in prognosis between the STD and ANH groups.

How does ANH affect the prognosis in PDAC patients who have undergone pancreatic resection? Direct and indirect effects can be assumed. One of the possible direct effects is the immunosuppressive effect of ANH (38). Additionally, compared to standard management, ANH is logically associated with circulatory overload. The only prospective RCT, in which every assessed ANH inpatient underwent PD, determined that ANH was related to greater intraoperative fluid management, and resulted in more pancreatic anastomotic complications (19). A similar trend was observed in this study as well. Postoperative complications may have a negative effect on survival outcomes in cancer patients (28,39,40), including PDAC (41,42). It has been suggested that postoperative complications could have immunosuppressive effects (39,40,43). Therefore, in terms of postoperative complications after ANH, immunosuppressive effects may be an additional consideration.

In our cohort, after PSM, the ANH group was associated with great intraoperative blood loss compared to the STD group. This trend was observed in a previous RCT of ANH in patients undergoing PD (19). Conversely, this trend was not observed in another liver surgery RCT (27). Several lines of evidence have shown an association between increased blood loss and poor outcomes in PDAC surgery (15,16,44). Our previous study also demonstrated those relationships (29). These data suggest that more intraoperative blood loss may negatively influence the prognosis of ANH. At the same time, we must be deliberate and critically consider that ANH can potentially cause increased intraoperative blood loss.

The present study has several limitations. First, this is a retrospective single-institution cohort study and not a randomized control trial. The patient population was not large. In this study, we performed propensity score matching using caliper matching, achieving a satisfactory balance of pre-ANH variables between the STD and

Table V. Comparison of clinicopathological characteristics after propensity score matching.

Characteristics	Post-match all (n=70)	STD (n=35)	ANH (n=35)	P-value	ASD
Sex, male	40 (57.1)	19 (54.3)	21 (60.0)	0.629	0.116
Age, years	69 (49-85)	69 (52-85)	69 (49-78)	0.668	0.146
Body mass index, kg/m^2	22.3 (14.1-33.3)	22.0 (18.8-28.4)	22.5 (14.1-33.3)	0.729	0.074
ASA-PS				0.324[b]	0.237
PS2	59 (84.3)	28 (80.0)	31 (88.6)		
PS3	11 (15.7)	7 (20.0)	4 (11.4)		
Preoperative biliary drainage	32 (45.7)	17 (48.6)	15 (42.9)	0.631	0.115
Laboratory values					
Hemoglobin, g/dl	12.9 (8.8-16.3)	12.5 (8.8-15.6)	13.6 (10.8-16.3)	0.011	0.675
CRP, mg/dl	0.20 (0.02-9.59)	0.16 (0.02-9.59)	0.27 (0.02-5.45)	0.375	0.068
Albumin, g/dl	3.9 (2.4-5.0)	3.8 (2.5-5.0)	4.0 (2.4-4.9)	0.110	0.193
Hemoglobin A1c, %	5.8 (4.4-11.8)	5.8 (4.4-11.8)	6.2 (4.4-9.0)	0.273	0.227
Creatinine, mg/dl	0.67 (0.41-1.30)	0.67 (0.43-1.21)	0.66 (0.41-1.30)	0.934	0.073
AST, U/l	32 (14-406)	36 (14-406)	27 (16-241)	0.526	0.131
ALT, U/l	45 (12-621)	51 (12-621)	35 (12-616)	0.991	0.105
Total bilirubin, mg/dl	0.8 (0.2-32.7)	0.8 (0.3-32.7)	0.9 (0.2-24.0)	0.684	0.093
CA19-9, U/ml	73 (1-9,675)	60 (1-3,199)	112 (5-9,675)	0.277	0.279
CEA, ng/ml	2.5 (0.5-37.0)	2.7 (0.7-37.0)	2.4 (0.5-23.9)	0.577	0.002
Operative variables					
Procedure				0.568[b]	0.256
Pancreaticoduodenectomy	50 (71.4)	26 (74.3)	24 (68.6)		
Distal pancreatectomy	19 (27.1)	9 (25.7)	10 (28.6)		
Total pancreatectomy	1 (1.4)	0 (0.0)	1 (2.9)		
Portal vein resection	9 (12.9)	4 (11.4)	5 (14.3)	>0.999[b]	0.085
Grouping of surgeons					
Junior surgeon	4 (5.7)	3 (8.6)	1 (2.9)	0.614[b]	0.248
Senior surgeon	66 (94.3)	32 (91.4)	34 (97.1)		
Pathology					
Tumor size, mm	28 (7-130)	26 (7-56)	30 (10-130)	0.331	0.344
UICC 8th edition					
T category				0.228[b]	0.420
T1	11 (15.7)	4 (11.4)	7 (20.0)		
T2	43 (61.4)	25 (71.4)	18 (51.4)		
T3	16 (22.9)	6 (17.1)	10 (28.6)		
T4	0 (0.0)	0 (0.0)	0 (0.0)		
N category				0.679	0.211
N0	30 (42.9)	16 (45.7)	14 (40.0)		
N1	25 (35.7)	13 (37.1)	12 (34.3)		
N2	15 (21.4)	6 (17.1)	9 (25.7)		
M category				0.284[b]	0.258
M0	61 (87.1)	32 (91.4)	29 (82.9)		
M1[a]	9 (12.9)	3 (8.6)	6 (17.1)		
UICC stage				0.061[b]	0.842
IA	8 (11.4)	3 (8.6)	5 (14.3)		
IB	13 (18.6)	11 (31.4)	2 (5.7)		
IIA	6 (8.6)	1 (2.9)	5 (14.3)		
IIB	25 (35.7)	13 (37.1)	12 (34.3)		
III	9 (12.9)	4 (11.4)	5 (14.3)		
IV	9 (12.9)	3 (8.6)	6 (17.1)		

Table V. Continued.

Characteristics	Post-match all (n=70)	STD (n=35)	ANH (n=35)	P-value	ASD
R0 resection	63 (90.0)	31 (88.6)	32 (91.4)	>0.999[b]	0.093

[a]All of the patients were diagnosed with M1 due to positive lymph nodes other than the regional lymph nodes. Continuous variables are presented as the median (range) and were analyzed using the Mann-Whitney U-test. Categorical variables are reported as the number (percentage) and were analyzed using the χ^2 test or Fisher's exact test, as appropriate. [b]Fisher's exact test was performed, while other comparisons for categorical variables were carried out using the χ^2 test. ALT, alanine aminotransferase; ANH, acute normovolemic hemodilution; ASA-PS, American Society of Anesthesiologists physical status; ASD, absolute standardized difference; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; STD, standard management; UICC, Union for International Cancer Control.

Table VI. Comparison of operative and postoperative outcomes after propensity score matching.

Outcomes	Post-match all (n=70)	STD (n=35)	ANH (n=35)	P-value
Operative results				
Procedure				0.568[b]
Pancreaticoduodenectomy	50 (71.4)	26 (74.3)	24 (68.6)	
Distal pancreatectomy	19 (27.1)	9 (25.7)	10 (28.6)	
Total pancreatectomy	1 (1.4)	0 (0.0)	1 (2.9)	
Portal vein resection	9 (12.9)	4 (11.4)	5 (14.3)	>0.999[b]
Operation time, min	310 (129-619)	261 (139-619)	327 (129-587)	0.042
Anesthesia time, min	374 (187-680)	368 (226-676)	392 (187-680)	0.086
Intraoperative blood loss, ml	728 (130-2,200)	570 (130-2,000)	970 (150-2,200)	<0.001
IBL >20% in CBV	33 (47.1)	10 (28.6)	23 (65.7)	0.002
Blood volume removed, ml	0 (0-800)	0 (0-0)	800 (400-800)	<0.001
Intraoperative fluid given, ml	3,700 (1,300-7,500)	3,200 (1,300-7.500)	4,000 (2,550-6,300)	<0.001
Intraoperative albumin, ml	0 (0-750)	0 (0-500)	0 (0-750)	0.138
Intraoperative FFP, ml	0 (0-0)	0 (0-0)	0 (0-0)	-
Intraoperative PC, ml	0 (0-0)	0 (0-0)	0 (0-0)	-
Total fluid volume administered, ml	4,075 (1,300-8,000)	3,200 (1,300-8,000)	4,850 (2,950-7,600)	<0.001
Intraoperative urine output, ml	500 (20-1,550)	430 (188-1,550)	530 (20-1,550)	0.332
Total in-out balance, ml	2,368 (485-5,500)	1,935 (485-5,500)	2,670 (1,190-4,555)	0.003
Total in-out balance, ml/kg/h[a]	6.5 (1.8-13.9)	6.3 (1.8-11.2)	6.6 (3.2-13.9)	0.104
Postoperative results				
Postoperative complications (Clavien-Dindo classification grade ≥3)	13 (18.6)	4 (11.4)	9 (25.7)	0.124[b]
Pancreatic fistula (ISGPF grade ≥B)	11 (15.7)	4 (11.4)	7 (20.0)	0.324[b]
Delayed gastric emptying (ISGPS grade ≥B)	9 (12.9)	3 (8.6)	6 (17.1)	0.477[b]
Postoperative hospital stay, days	17 (6-64)	17 (8-61)	19 (6-64)	0.101
Adjuvant chemotherapy	54 (78.3)	29 (82.9)	25 (73.5)	0.348

[a]Estimated using the following formula: Total in-out balance/body weight (kg)/anesthesia time (h). Continuous variables are presented as the median (range) and were analyzed using the Mann-Whitney U-test. Categorical variables are reported as the number (percentage) and were analyzed using the χ^2 test or Fisher's exact test, as appropriate. [b]Fisher's exact test was performed, while other comparisons for categorical variables were carried out using the χ^2 test. ANH, acute normovolemic hemodilution; CBV, circulating blood volume; FFP, fresh frozen plasma; IBL, intraoperative blood loss; ISGPF, the International Study Group of Pancreatic Fistula; ISGPS, the International Study Group of Pancreatic Surgery; PC, platelet concentration; STD, standard management.

ANH groups. However, despite our best efforts, there are instances where standardized difference scores exceed 0.2 for certain variables. One possible explanation for this is that large variations in certain variables, such as CA19-9, may contribute to such an imbalance. In addition, not having a large sample size may have created a non-ideal balance

after PSM. These results speak to the desirability of a larger sample size for achieving optimal balance. However, if we had added the borderline resectable PDAC cohort to the current resectable PDAC cohort, the borderline cases would have greatly increased the ANH group due to the estimated increased blood loss associated with vascular resection. Adding borderline cases, however, would make it difficult to validate the true impact of ANH on long-term outcomes in PDAC patients. Moreover, typical study biases, such as fluid overloading, more intraoperative blood loss, longer operation time, etc., were not excluded from this study. These biases make drawing definitive conclusions difficult. Nonetheless, there have been no previous studies examining the effect of ANH on the long-term prognosis of PDAC. Accordingly, the suggestions from this study should not be ignored.

In conclusion, the present study, using PSM analysis, showed that ANH could be associated with poor postoperative long-term outcomes in resectable PDAC patients compared to STD. Various biases make it difficult to conclude whether or not ANH is inherently harmful. However, the one thing we can say without hesitation is that management without transfusion is the best course of action. Furthermore, ABT has the worst negative impact. Thus, we should make every effort to avoid ABT, and ANH is certainly a valuable approach to achieve this goal. In general, at least until a definitive conclusion is reached, it is better to limit the use of ANH in certain specific PDAC cases.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TW, KI, NK and KHa contributed to the study conception and design. TW, KI, NK, HN and KHa performed surgical resection. TW, KI, NK, HN, TK, SK, HF, YT, TY, KC, JS, KHi and KHa collected the clinical data. TW, KI, NK, HN, TK, SK, HF, YT, TY, KC, JS, KHi and KHa analyzed and interpreted the data. TW wrote the first draft of the manuscript. KI, NK, HN, TK, SK, HF, YT, TY, KC, JS, KHi and KHa contributed to the review and/or critical revision of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TW and KI confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine (reference no. 2022-032; Aomori, Japan). Informed consent was obtained in the form of an opt-out feature on our website, with the approval of the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine. The present study did not include minors. The present study was designed and carried out in accordance with the Declaration of Helsinki.

Patient consent for publication

Informed consent for publication was obtained in the form of an opt-out feature on our website, with the approval of the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine (Aomori, Japan).

Competing interests

The authors declare that they have no competing interests.

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