Journal of Gastrointestinal Surgery (2018) 22:1715–1723
https://doi.org/10.1007/s11605-018-3829-3

ORIGINAL ARTICLE

Synergistic Effects of Perioperative Complications on 30-Day Mortality Following Hepatopancreatic Surgery

Katiuscha Merath[1] · Qinyu Chen[1] · Fabio Bagante[1,2] · Ozgur Akgul[1] · Jay J. Idrees[1] · Mary Dillhoff[1] · Jordan M Cloyd[1] · Timothy M. Pawlik[1,3]

Received: 25 April 2018 / Accepted: 22 May 2018 / Published online: 18 June 2018

Abstract

Background Data on the interaction effect of multiple concurrent postoperative complications relative to the risk of short-term mortality following hepatopancreatic surgery have not been reported. The objective of the current study was to define the interaction effect of postoperative complications among patients undergoing HP surgery on 30-day mortality.

Methods Using the ACS-NSQIP Procedure Targeted Participant Use Data File, patients who underwent HP surgery between 2014 and 2016 were identified. Hazard ratios (HRs) for 30-day mortality were estimated using Cox proportional hazard models. Two-way interaction effects assessing combinations of complications relative to 30-day mortality were calculated using the relative excess risk due to interaction (RERI) in separate adjusted Cox models.

Results Among 26,824 patients, 10,886 (40.5%) experienced at least one complication. Mortality was higher among patients who experienced at least one complication versus patients who did not experience a complication (3.0 vs 0.1%, $p < 0.001$). The most common complications were blood transfusion (16.9%, $n = 4519$), organ space infection (12.2%, $n = 3273$), and sepsis/septic shock (8.2%, $n = 2205$). Combinations associated with additive effect on mortality included transfusion + renal dysfunction (RERI 12.3, 95% CI 5.2–19.4), pulmonary dysfunction + renal dysfunction (RERI 60.9, 95% CI 38.6–83.3), pulmonary dysfunction + cardiovascular complication (RERI 144.1, 95% CI 89.3–199.0), and sepsis/septic shock + renal dysfunction (RERI 11.5, 95% CI 4.4–18.7).

Conclusion Both the number and specific type of complication impacted the incidence of postoperative mortality among patients undergoing HP surgery. Certain complications interacted in a synergistic manner, leading to a greater than expected increase in the risk of short-term mortality.

Keywords Complication · Hepatectomy · Pancreatectomy · Mortality

Introduction

Hepatopancreatic (HP) surgery involves complex procedures that are associated with a high risk for perioperative complications.[1,2] Even though mortality associated with HP surgery has decreased substantially over the past several decades, the risk of complications remains relatively high.[1,3–5] The causes of complications are multifactorial with many studies reporting patient-, disease-, operative-, hospital-, and even social-specific factors that influence risk of morbidity.[6–10] Previous research has largely focused on the impact of a single, specific postoperative complication on mortality risk. For example, Silber et al. reported that the development of any first postoperative complication was associated with, on average, a threefold increased odds of death.[11] Many patients, however, experience multiple

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-018-3829-3) contains supplementary material, which is available to authorized users.

✉ Timothy M. Pawlik
tim.pawlik@osumc.edu

1 Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, OH, USA

2 Department of Surgery, University of Verona, Verona, Italy

3 Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, Columbus, OH, USA

complications following major surgery. Data on the interaction effect of multiple concurrent postoperative complications relative to the risk of short-term mortality following HP surgery have not been reported. As such, the objective of the current study was to define the interaction effect of common and procedure-specific postoperative complications among patients undergoing HP surgery on 30-day mortality using a cohort of patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).

Materials and Methods

Data Sources and Study Population

Using the ACS-NSQIP Participant Use Data File (PUF) and the Procedure Targeted PUF, patients who underwent pancreatic and hepatic surgery between 2014 and 2016 were identified. Information in the final dataset included demographic characteristics, preoperative comorbidities, and perioperative clinical variables, as well as 30-day postoperative complications and mortality data. Eligible patients were selected based on Current Procedural Terminology codes (Supplementary Table 1). Patients who were outpatient ($n = 208$) or had the following preoperative comorbidities were excluded: acute renal failure/dialysis ($n = 106$), mechanical ventilation ($n = 18$), pneumonia ($n = 0$), preoperative sepsis ($n = 341$), wound infection ($n = 159$), and transfusions ($n = 163$). In addition, patients with missing data on weight ($n = 63$), height ($n = 86$), ASA status ($n = 43$), functional dependence ($n = 62$), operation time ($n = 13$), or the occurrence of pancreatic fistula ($n = 162$), delayed gastric emptying ($n = 313$), post-hepatectomy liver failure (PHLF) ($n = 90$), or bile leak ($n = 0$) were excluded. Finally, individuals who died on the day of surgery ($n = 19$) were excluded. The study did not require access to protected health information and therefore was exempt from review by The Ohio State University Institutional Review Board.

Outcomes

The primary outcome was the occurrence of 30-day mortality, which was defined as patient death within 30 days of the index operation. Six major common perioperative complications were evaluated: transfusion, organ space infection (OSI), sepsis/septic shock, pulmonary dysfunction, renal dysfunction, and cardiovascular complications. Certain outcomes were composite measures of more than one separate ACS-NSQIP outcome due to the low frequency of the individual metric. For example, pulmonary dysfunction was categorized as pneumonia, deep vein thrombosis (DVT) and pulmonary embolus (PE), unplanned intubation, and prolonged mechanical ventilation. Renal dysfunction included urinary tract infection (UTI), progressive renal insufficiency, and acute renal failure. Cardiovascular complications were defined as myocardial infarction, cardiac arrest, and cerebrovascular accident. For patients undergoing pancreatectomy, two procedure-specific complications were examined: pancreatic fistula and delayed gastric empting. Similarly, for patients undergoing hepatectomy, bile leak and PHLF were recorded. The definitions for these parameters in NSQIP are well established national/international criteria and can be found in the NSQIP code handbook.

Statistical Analysis

Patient characteristics and preoperative comorbidities were compared among patients who did not experience a postoperative complication versus patients who had at least one complication. The Pearson chi-square test was used to compare categorical variables and the Kruskal-Wallis rank test for continuous variables. The incidence of overall 30-day mortality among patients who experienced each of the major complications was analyzed. The Cox proportional hazard model was used to estimate the hazard ratios (HRs) with 95% confidence intervals (CI) for 30-day mortality.[12] The two-way interaction effects of each combination of two complications on 30-day mortality were calculated using the relative excess risk due to interaction (RERI) in separate adjusted Cox models.[13] As previously reported, the RERI method determines whether there is additive interaction in models that are inherently multiplicative, with additive interaction being the empirical method to determine biological interaction.[14] All results were adjusted for age, sex, race, body mass index, emergency procedure, functional dependence, dyspnea, chronic obstructive pulmonary disease, current smoking, congestive heart failure, ascites, cancer, steroid use, bleeding disorder, preoperative hematocrit, procedure category, and log (operative time). Two-sided p values < 0.05 were used to evaluate statistical significance. All statistical analysis was performed with STATA 14.0 MP.

Results

Preoperative Characteristics of Patients

Among 26,824 patients included in the study, 10,886 (40.5%) experienced at least one complication while 15,938 (59.5%) did not experience any postoperative complication (Table 1). The average age of patients who experienced at least one complication was 62 years; patients who experienced a complication were more likely to be female and non-white. The majority of patients who experienced a complication were ASA class 3 and were more likely to have preoperative risk factors such as diabetes, COPD, anemia, and functional dependence. Postoperative complications were more common

Table 1 Characteristics of patients undergoing pancreatic and hepatic surgery

	No complication		Complication		*P* value
	15,938		10,886		
Age (years)	60.4	13.6	62.7	12.8	< 0.001
Female	8378	52.6	5157	47.4%	< 0.001
Race					<0.001
White	2131	13.4	1437	13.2	
Non-white	11,751	73.7	7815	71.8	
Unknown	2056	12.9	1634	15.0	
ASA class					< 0.001
1	244	1.5	67	0.6	
2	4554	28.6	2291	21.1	
3	10,391	65.2	7640	70.2	
4	746	4.7	887	8.2	
5	3	0.1	1	0.1	
Body mass index (kg/m^2)	27.9	6.1	28.2	6.3	< 0.001
Emergency	40	0.3	31	0.3	0.597
Diabetic	3148	19.8	2619	24.1	< 0.001
Dyspnea	681	4.3	693	6.4	< 0.001
Chronic obstructive pulmonary disease	521	3.3	537	4.9	< 0.001
Current smoker	2720	17.1	1893	17.4	0.491
Congestive heart failure	29	0.2	56	0.5	< 0.001
Hypertension	7354	46.1	5803	53.3	< 0.001
Functionally dependent	83	0.5	106	1.0	< 0.001
Ascites	40	0.3	59	0.5	< 0.001
Hematocrit					< 0.001
Low ≤ 34	1926	12.1	2455	22.6	
Medium 34–44	11,527	72.3	7089	65.2	
High ≥ 44	2132	13.4	1179	1.8	
Hct missing	353	2.2	163	1.5	
Steroid use	422	2.7	372	3.4	< 0.001
Cancer	8642	54.2	5837	53.6	0.33
Bleeding disorder	406	2.6	383	3.5	< 0.001
Procedure type					< 0.001
Hepatic surgery	7204	45.2	3355	30.8	
Pancreatic surgery	8734	54.8	7531	69.2	
Chemotherapy*	1228	14.1	1100	14.6	0.294
Radiation therapy*	521	6.0	465	6.2	0.401

*Only in patients undergoing pancreatectomy

among patients who underwent pancreatectomy than hepatectomy (69.2 vs 30.8%, $p < 0.001$).

Perioperative Complications and 30-Day Mortality

Overall, 30-day mortality was 1.3%; mortality was higher among patients who experienced at least one complication versus patients who did not experience a complication (3.0 vs 0.1%, $p < 0.001$) (Table 2). The most common complications were blood transfusion (16.9%, $n = 4519$), organ space infection (12.2%, $n = 3273$), and sepsis/septic shock (8.2%, $n = 2205$). Among patients who underwent pancreatic resection, pancreatic fistula was observed in 18.3% ($n = 2967$), while 12.5% ($n = 2039$) had delayed gastric emptying. Bile leak and PHLF were observed in 7.7% ($n = 817$) and 5.2% ($n = 549$) of patients who underwent liver resection, respectively. The incidence of postoperative mortality varied based on type of complication and was highest among patients who developed a cardiovascular event (34.4%, $n = 165$), PHLF (12.4%, $n = 68$), and pulmonary dysfunction (11.1%, $n = 246$) (Table 2). On univariable analysis, the occurrence of each type of complication was associated with an increased risk of 30-day mortality (Table 3). For example, organ space infection (HR 2.8, 95% CI 2.27–3.66) was associated with a roughly 3-fold increased risk of perioperative death. On multivariable analysis, after adjusting for risk factors, each specific complication remained associated with 30-day mortality, including organ space infection (HR 2.17, 95% CI 1.70–2.78) and cardiovascular complications (HR 38.26, 95% CI 30.27–48.37) (all $p < 0.001$).

Impact of Postoperative Complications on Mortality

Among patients who developed a complication, 54.4% had only one complication, while 23.4, 12.0, 6.0, and 4.3% of patients had two, three, four, or five to eight complications, respectively (Fig. 1a). In addition, postoperative mortality increased exponentially with the concomitant increase in the

Table 2 Perioperative complications and rate of mortality among patients undergoing pancreatic and hepatic surgery

	Complication		Mortality among complication	
	N	%	*N*	%
Total sample	26,824	345	1.3	
Composite morbidity	10,886	40.6	324	3.0
Transfusion	4519	16.9	164	3.6
Organ space infection	3273	12.2	93	2.8
Sepsis/septic shock	2205	8.2	147	6.7
Pulmonary dysfunction	2208	8.2	246	11.1
Renal dysfunction	1031	3.8	111	10.8
Cardiovascular complications	480	1.8	165	34.4
Pancreatic fistula*	2967	18.3	62	2.1
Delayed gastric empting*	2039	12.5	65	3.2
Bile leak#	817	7.7	33	4.0
Post hepatectomy liver failure#	549	5.2	68	12.4

*Only assessed among patients who had pancreatic procedures

Only assessed among patients who had hepatic procedures

Table 3 Unadjusted and adjusted Cox proportional hazards models for 30-day mortality among patients undergoing hepatic and pancreatic surgery

Complication	Complication only			Complication and risk factors[1]		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Transfusion	4.17	3.35–5.19	< 0.001	2.83	2.22–3.61	< 0.001
Organ space infection	2.88	2.27–3.66	< 0.001	2.17	1.70–2.78	< 0.001
Sepsis/septic shock	9.27	7.45–11.53	< 0.001	6.65	5.29–8.35	< 0.001
Pulmonary dysfunction	34.47	26.86–44.22	< 0.001	26.66	20.61–34.50	< 0.001
Renal dysfunction	13.59	10.81–17.09	< 0.001	10.56	8.32–13.39	< 0.001
Cardiovascular complications	57.89	46.54–72.02	< 0.001	38.26	30.27–48.37	< 0.001
Pancreatic fistula*	2.00	1.48–2.70	< 0.001	1.89	1.40–2.56	< 0.001
Delayed gastric empting*	3.35	2.50–4.51	< 0.001	2.50	1.84–3.38	< 0.001
Hepatic complication bile leakage*	4.32	2.90–6.43	< 0.001	2.40	1.58–3.65	< 0.001
Post hepatectomy liver failure*	22.17	15.60–31.51	< 0.001	13.03	8.92–19.03	< 0.001

Each Cox model includes only one perioperative complication variable (i.e., separate Cox model for each complication were generated)

HR hazard ratio, *CI* confidence interval

*For hepatic or pancreatic specific complications, we investigated their effects only among patients undergoing hepatic or pancreatic procedures, separately

[1] Risk factors are age, sex, race, body mass index, emergency, functional dependence, dyspnea, chronic obstructive pulmonary disease, current smoking, congestive heart failure, ascites, cancer, steroid use, bleeding disorder, hematocrit, procedure category, and log (operative time)

number of complications (Fig. 1b). Specifically, patients without complications had a mortality of 0.1 versus 0.6% for patients with one complication, 2.7% for patients with two complications, 5.0% for those with three complications, 9.6% in patients with four complications, and 20.4% among patients who experienced 5–8 complications. To analyze the interactions among the various types of postoperative complications, the possible synergistic effects of eight different complication combinations on 30-day mortality was examined (Table 4). The combinations associated with a positive additive effect on mortality included: transfusion + renal dysfunction (RERI 12.3, 95% CI 5.2–19.4), pulmonary dysfunction + renal dysfunction (RERI 60.9, 95% CI 38.6–83.3), pulmonary dysfunction + cardiovascular complication (RERI 144.1, 95% CI 89.3–199.0), renal dysfunction + cardiovascular complication (RERI 48.5, 95% CI 10.6–86.3), sepsis/septic shock + pulmonary dysfunction (RERI 13.3, 95% CI 2.6–24.0), and sepsis/septic shock + renal dysfunction (RERI 11.5, 95% CI 4.4–18.7). The combination with the strongest synergistic effect on mortality was pulmonary dysfunction + cardiovascular complication, followed by the combination of pulmonary dysfunction + renal dysfunction. On the other hand, the most common combinations observed in the cohort were organ space infection + sepsis/septic shock ($n = 1382$, 5.1%), followed by pulmonary dysfunction + sepsis/septic shock ($n = 800$, 2.9%) and pulmonary dysfunction + renal dysfunction (1.3%, $n = 349$) (Table 5). The interactions among various types of postoperative complications among pancreatic (Supplementary Table 2) and hepatic (Supplementary Table 3) only patients were also examined. In particular, there was a synergistic effect of PHLF with pulmonary and renal dysfunction among patients undergoing hepatic resection.

Discussion

Postoperative complications have a significant and deleterious impact on patient-reported experiences, hospital costs, cancer recurrence, and perioperative mortality.[15,16,2,17,1,18] Therefore, an enhanced understanding of the relationship between postoperative complications and risk of mortality is important to improve outcomes among patients undergoing major HP surgery. In this population-based study, the interaction effects among postoperative complications and the derivative impact on postoperative mortality were defined. Among the over 10,000 patients who experienced at least one complication, almost half of all patients experienced multiple complications. In turn, while overall mortality associated with HP surgery was low (< 2%), risk of death was strongly associated with postoperative complications. In fact, the risk of mortality incrementally increased as the number of postoperative complications increased. Data from the current study demonstrated that the increase in mortality associated with multiple complications was exponential, rather than additive in nature. The relative excess risk due to interaction (RERI) was determined among patients who developed multiple complications and the final mortality risk was noted to be greater than the simple sum of the individual mortality risks.[13] Specifically, while mortality was only 0.6% among patients who experienced one complication, the incidence of mortality grew to almost

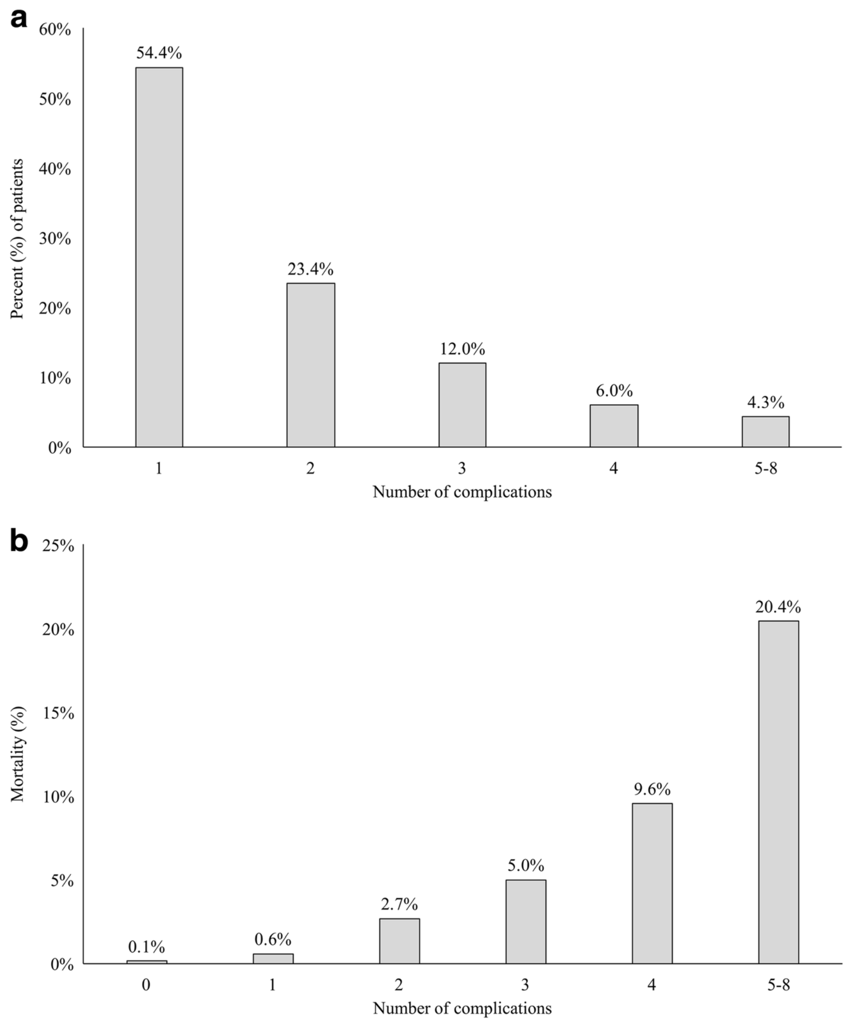

Fig. 1 **a** Number of complications among patients experiencing at least one complication following liver and pancreatic surgery. **b** Rate of 30-day mortality according to the number of complications

10% among patients who had four complications. The type of complications also affected mortality, as several specific combinations of complications had a synergistic effect that led to an observed mortality risk greater than would have been expected (Table 4). Collectively, the data demonstrated that complications were not independent events; rather, multiple complications—and specific combinations of complications—significantly altered mortality risk associated with HP surgery. Both the number of complications and the specific type of complication(s) can influence risk of mortality following a surgical procedure.[17,19] Furthermore, complications are not independent events; rather, index complications can markedly alter a patient's subsequent risk of developing additional complications.[20,21] For example, Kim et al. reported that multiple complications increased the risk of other perioperative complications.[22] Specifically, the development of acute kidney injury (AKI), acute respiratory failure, or sepsis/septic shock alone increased the risk of developing the other two complications.[22] In another study, Tevis et al. reported on the interactions between specific complications among patients who underwent a range of general surgical procedures.[23] In this study, the authors reported an over fourfold increase in mortality among patients who had multiple complications compared with patients who had only 0–1 complication.[23] Certain complications such as coma, septic shock, and failure to wean off the ventilator were strongly correlated with subsequent additional complications. In a separate study, Varley et al. reported that each additional complication that a patient experienced after pancreaticoduodenectomy was associated with a 48% increased odds of death (OR 1.48, 95% CI, 1.31–1.58).[24] In the current study, both the number (Fig. 1b) and type of complication (Table 3) strongly correlated with risk of mortality among patients undergoing HP surgery. Indeed, the adjusted risk of death was strongly associated with cardiovascular complications, pulmonary dysfunction, and PHLF. Furthermore, 30-day mortality exponentially increased from 0.6% among patients with one complication to 20.4% among patients who had five or more complications. Collectively, the data strongly suggest that complications have a synergistic effect on mortality in the perioperative period. In turn, identification and prevention of early complications may be important in preventing a cascading risk of subsequent complications and increased mortality.

Table 4 Relative excess risk due to interaction for 30-day postoperative mortality based on adjusted Cox proportional hazards models of the occurrence of two perioperative complications among patients undergoing hepatic and pancreatic procedures

		Transfusion					Organ space infection					Sepsis/septic shock			
		HR	95% CI				HR	95% CI				HR	95% CI		
Organ space infection	TRA	2.5	1.8	3.5											
	OSI	3.1	2.3	4.1											
	TRA&OSI	4.9	3.4	7.0											
	RERI	0.3	-1.4	2.0											
Sepsis/septic shock	TRA	8.0	5.9	10.8		OSI	8.2	6.1	11.1						
	SEP	3.1	2.2	4.2		SEP	0.9	0.5	1.5						
	TRA&SEP	13.4	9.6	18.7		OSI&SEP	5.6	4.2	7.4						
	RERI	3.4	-0.5	7.3		RERI	2.5	0.0	5.0	*					
Pulmonary dysfunction	TRA	34.6	24.7	48.4		OSI	30.5	22.9	40.7		SEP	28.7	21.0	39.4	
	PUL	3.1	2.0	4.9		PUL	1.6	0.9	2.8		PUL	5.4	3.4	8.8	
	TRA&PUL	44.3	30.9	63.7		OSI&PUL	24.7	17.7	34.6		SEP&PUL	46.5	33.6	64.2	
	RERI	7.6	-3.6	18.9		RERI	-6.3	-13.8	1.2		RERI	13.3	2.6	24.0	*
Renal dysfunction	TRA	9.3	6.6	13.1		OSI	10.6	8.0	14.2		SEP	9.6	6.8	13.7	
	REN	2.4	1.8	3.2		REN	1.9	1.4	2.6		REN	5.5	4.1	7.3	
	TRA&REN	23.0	16.5	31.9		OSI&REN	15.3	10.8	21.7		SEP&REN	25.7	19.0	34.7	
	RERI	12.3	5.2	19.4	*	RERI	3.8	-1.6	9.1		RERI	11.5	4.4	18.7	*
Cardiovascular complication	TRA	69.6	51.1	94.9		OSI	54.9	41.8	72.1		SEP	66.3	48.8	90.1	
	CV	3.9	2.9	5.4		CV	2.8	2.0	3.8		CV	9.2	6.8	12.5	
	TRA&CV	59.0	41.1	84.7		OSI&CV	36.6	25.0	53.6		SEP&CV	85.9	61.0	121.0	
	RERI	-13.5	-35.8	8.7		RERI	20.1	3.7	36.4	*	RERI	11.4	-14.9	37.7	
		Pulmonary dysfunction					Renal dysfunction								
		HR	95% CI				HR	95% CI							
Renal dysfunction	PUL	3.7	1.9	7.5											
	REN	20.1	15.0	26.8											
	PUL&REN	83.8	61.4	114.3											
	RERI	60.9	38.6	83.3	*										
Cardiovascular complication	PUL	36.2	22.2	59.0		REN	52.0	39.3	68.9						
	CV	20.8	15.1	28.6		CV	14.4	10.6	19.6						
	PUL&CV	200.1	144.9	276.3		REN&CV	113.9	78.7	164.9						
	RERI	144.1	89.3	199.0	*	RERI	48.5	10.6	86.3	*					

TRA transfusion, *OSI* organ space infection, *SEP* sepsis/septic shock, *PUL* pulmonary dysfunction, *REN* renal dysfunction, *CV* cardiovascular complication

*Statistically significant interaction

Table 5 Frequency of specific complication combinations, with significant synergistic interactions, among patients undergoing hepatic and pancreatic surgery

Total sample	Total		Mortality	
	N (26,824)	%	*n*	%
Positive interactions				
Transfusion—renal dysfunction	319	1.19	66	20.7
Sepsis/septic shock—pulmonary dysfunction	800	2.98	123	15.4
Sepsis/septic shock—renal dysfunction	345	1.29	67	19.4
Pulmonary dysfunction—renal dysfunction	349	1.30	102	29.2
Pulmonary dysfunction—cardiovascular complications	265	0.99	129	48.7
Renal dysfunction—cardiovascular complications	83	0.31	44	54.0
Negative interactions				
Organ space infection—sepsis/septic shock	1382	5.15	79	5.7
Organ space infection—cardiovascular complications	142	0.53	38	26.8
Interaction with liver specific complication	*N* (10,599)	%	*n*	%
Positive interactions				
Liver failure—pulmonary dysfunction	211	1.99	59	28.0
Liver failure—renal dysfunction	112	1.06	42	37.5

*No statistically significant synergistic complication combinations were observed among patients undergoing pancreatectomy

Research on the underlying mechanisms associated with the interactions among complications is scarce. In particular, data on which complications interact synergistically to elevate the risk of mortality remain poorly defined. Kim et al. reported synergistic interactions among AKI, acute respiratory failure (ARF), sepsis/septic shock, and stroke among patients undergoing general surgery procedures.[25] The authors theorized that multifactorial mechanisms including biological, clinical, and social factors were responsible. In addition, the management of one complication may lead to or exacerbate a subsequent complication. For example, aggressive resuscitation of bleeding (via transfusion) or AKI (via intravenous fluids) may lead to pulmonary complications. Complex physiopathological process may also contribute to inter-organ "crosstalk"—i.e., the adverse effect of one malfunctioning organ on the function of another.[26] Crosstalk among organ systems can particularly occur related to kidney, lung, heart, brain, and liver dysfunction.[27,26,28–30] In turn, perturbation of an individual process can increase the risk of developing a subsequent complication in a new distant organ system. To this point, we investigated the synergistic effects of specific combinations of complications on death by measuring the relative excess risk due to interaction (RERI). Indeed, several combinations of complications elevated the risk of death greater than expected such as pulmonary dysfunction + renal dysfunction, pulmonary dysfunction + cardiovascular complication, sepsis/septic shock + pulmonary dysfunction, and sepsis/septic shock + renal dysfunction. Furthermore, among patients undergoing hepatectomy, PHLF interacted synergistically with pulmonary and renal dysfunction to markedly increase mortality. Further research is needed to elucidate the mechanisms that underlie the interactions among postoperative complications and identify ways to intervene in the deadly cascade associated with multiple complications.

The consistent and accurate classification of postoperative outcomes has important implications on hospital accreditation, quality initiatives, and research endeavors. Currently, the Clavien-Dindo grading system is the most widely adopted complication scoring system. The Clavien-Dindo system assigns a score of I-V based on the severity of the worst postoperative complication experienced by the patient.[31] The Clavien-Dindo system is, however, an ordinal scale and fails to take into account that potential important differences in severity between the complication grades. For example, grade I versus II complications may not equal the differences between grade II and III complications; in addition, all grade III complications may not be equal in severity. In addition, the system is predicated on just one complication (i.e., the "most severe" complication). These limitations have led to the development of other complication schemes such as the comprehensive complication index (CCI).[32] Data from the current study highlight the importance of the number, severity, and specific types of complications that occur in the postoperative period and suggest that the CCI, or grading systems like it, may be more appropriate for research and quality initiatives. The ability to rescue patients after major postoperative complications has also been increasingly identified as an important metric of high quality hospitals. Rescue from complications is especially important following HP surgery as morbidity can be high—the incidence of complications was 40.5% in the current study.[33–35] In particular, the occurrence of multiple complications can be a strong risk factor for failure to rescue following HP surgery.[24] The ability to rescue patients from multiple complications, especially complications that have a synergistic and deleterious effect, should be the focus of quality and safety initiatives.

The current study had several limitations. Similar to other studies that utilized administrative data, there are inherent limitations to the ACS-NSQIP dataset.[36] Specifically, data on complications were pre-determined according to the ACS-NSQIP catalog and the definitions established by ACS-NSQIP. However, standard variable definition and rigorous clinical abstraction available through the ACS-NSIQP provided reliable and valid surgical outcomes assessment measures.[37] Complication data collected through the ACS-NSQIP are also generally more accurate than data obtained from administrative, claims data sources.[38,39] Due to the very low frequency of certain complications, some outcomes were analyzed as composite measures rather than as separate entities. While these complications were grouped according to the organ system involved or common underlying physiopathology, future studies will need to evaluate the impact of individual complications such as myocardial infarction, stroke, or pulmonary embolism. The exact etiology of each complication and its specific contribution to death could also not be directly assessed. Therefore whether complications and mortality were a result of disease stage, overall health status, underlying liver disease, or a combination of all these factors could not be fully elucidated.

In conclusion, both the number and specific type of complication impacted the incidence of postoperative mortality among patients undergoing HP surgery. Furthermore, certain complications interacted in a synergistic manner, leading to a greater than expected increase in the risk of short-term mortality. Further studies are needed to better understand the biological, clinical, and psychosocial factors that underlie the synergistic interactions between postoperative complications. A high level of vigilance in the postoperative period may facilitate early identification of patients at risk for multiple complications, thereby rescuing these patients early on and reducing postoperative mortality following major liver and pancreatic surgery.

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